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LIGHT FROM THE BOTANIC FIELD ON MEDICAL MYCOLOGIC PROBLEMS *

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Owing to the example and interest of Dr. Milton B. Hartzell, I have been more or less actively engaged in the study of the higher fungi for nearly twelve years. During this time, I have passed through the three stages of the development of any specialist. I refer here to the classification of my former professor of anatomy, Dr. George A. Piersol, who told his students that there were three stages in the development of the anatomist: (1) that of the primitive student who felt that he could never know anything about anatomy; (2) that of the young graduate, or even instructor, who felt that he knew everything about the subject, and finally, (3) the inevitable and true realization, born of bitter experience, that one can never hope to know much about anatomy. I feel that I have arrived at the third stage of mycology, in view of having passed through the first two stages, and that I am now in the final one of discouragement, indeed pessimism, about knowing all that should be known on the subject.

Recently I have been wondering what attitude the practicing dermatologist, too, or even the average and not necessarily mycologically inclined laboratory man must have toward the subject. I can envisage the general practitioner poring over the toes of his patient, making brave attempts to culture the fungus, and finally giving up further work in disgust when he arrives at the finals and attempts to determine the species of the organism. I have gone through all of this myself. I wonder whether he is not indeed suspicious about the whole business. He encounters, for instance, the utmost vagueness in almost every mycologic report, or even reads, when the author reaches the section on classification, that "the classification of the fungi is notoriously unsatisfactory" and "the variability in morphology of fungi is extreme, depending upon the particular culture media employed," etc. I marvel a little that there has not been further rebellion all along the line, or

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even a general uprising; yet the only murmurs bordering on discontent at the present trend of mycology that I have heard were from Dr. Walter Highman. Among his many philosophic and constructive utterances he once said, "Mycological research still seems to be engaged in a field which Sabouraud long ago exhausted."

All these thoughts prompt me to action, and I hope this communication will draw the curtain from the scenes and screen some of the considerations which make mycology such a difficult and unsatisfactory subject. I cannot do this as fully as I should like, so I shall content myself with one or two phases recently developed by botanists and not generally known even to dermatomycologists. These, if finally established as scientific facts, will practically revolutionize medical mycology, not only taxonomically but immunologically, diagnostically and therapeutically. Before proceeding, I shall voice a certain satisfaction at the patience which the dermatologic and other professions have exercised with the comparatively slow development of mycologic research.

SOME DERMATOMYCOLOGIC DISCREPANCIES

Before unfolding the work of these botanists, I shall cite a few dermatologic experiences in which discrepancies have arisen and which will lead the dermatologist to interdigitate better with the botanist. The only phase of the subject that I shall treat is that connected with morphology. I have selected it because it is so fundamental; it is the portal of entry to the other phases.

Powderiness of Colonies.—A number of years ago I[1] read a short paper before the American Dermatological Association and showed lantern slides of cultures obtained from my personal case of ringworm of the toes. The point to this presentation was that whereas for many years the colony, on repeated trials, had been of a soft duveteuse character, eventually a colony cropped up which was powdery. All of these were primary cultures direct from my toes. This was, of course, nothing more nor less than the old story of variability in the morphology of fungus cultures; but the particular point to the phenomenon was its occurrence in tissue as well as in the test tube.

The foregoing situation will be understood better if I translate it into terms of the microscope. Thus, the property of downiness in a colony (duveteuseness) is referable to the felting of mycelium which comprises the colony; powderiness is referable to spores, including fuseaux, providing they appear on or above the surface of the colony and are not hidden by the mycelial underbrush. What had happened in the culture of my own toe was nothing more nor less than a sudden (atavistic?) penchant for the production of spores. Now, it so happens

1. Weidman, F. D.: Morphologic Variations in a Ringworm Species of the Toes, Arch. Dermat. & Syph. **13**: 374 (March) 1926.

that the classification of dermatophytes depends in large part on the appearance of the colony grossly. If duveteuse, for instance, it will be referred to *Tr. niveum;* if powdery (not to go into such a classification exhaustively), to the gypseum group. Hence, I was in a quandary as to the classification of the species obtained from my toe. This situation is encountered at all times, is most disconcerting and is responsible for Ota and Langeron's [2] recent classification, in which they depend exclusively on the microscopic features as they appear in the hanging drop as the basis for classification.

Pigment Production.—Again, all dermatomycologists have encountered cultures of *Trichophyton violaceum,* in which color development was most capricious. The variation did not consist so much in that the colony in one tube would be pigmented whereas the duplicate planting in another would not show any such pigmentation, but in that a portion of a given colony would be pigmented through 75 per cent of its periphery, whereas the remaining segment would not show any pigment. A further variant of the same feature is experienced in numerous yeast colonies. Not uncommonly the greater part of the colony will have a brown, pasty appearance, while a certain segment of the same colony will be porcelain white and glistening and evidently of different texture from the rest of the colony.

Hanging Drops.—One of the most annoying of these vagaries comes to light in the hanging drop preparations. It is the routine practice in the laboratory to make four hanging drop preparations of each species of which a determination is attempted. This is necessary, not on account of difficulty in securing growth, but because the appearances in the different hanging drops may be different; that is, although one employs dextrose bouillon from the same test tube, selects the explants from the same portion of the colony, and keeps the preparation in the same environment throughout, one may nevertheless discover at the end of the routine ten days that some of the hanging drops will exhibit fuseaux and spirals, whereas others will not. Indeed, even after observation over two or three months, the fuseaux and spirals may never develop.

The foregoing data represent only a few examples of the discrepancies which consistently recur in hanging drops and which will occur even under strictest controls; these are sufficient, however, to show why it is difficult or dangerous to essay to identify species, and particularly dangerous or even scientifically dishonest to describe new species in the strict botanic sense on such insufficient evidence as minor variations in the hanging drop. I have personally described only two new fungus species in all my experience—both of these came from an

2. Ota, M., and Langeron, M.: A New Classification of the Dermatophytes, Ann. de parasit. **1**: 305 (Oct.) 1923.

exfoliative dermatitis of a rhinoceros—and it was only in view of the unusual habitat that I felt I was safe in my action.

Effect of Habitat.—I shall cite an additional instance of this variability in fungi which will be recognized at once as a familiar fact, and which will bring the situation home. I refer to blastomycosis and coccidioidal granuloma. As dermatomycologists, of course, know, these organisms do not produce mycelium in tissue, whereas on artificial mediums they do. This is such an extreme and constant variation that it does not complicate the work on human beings; the more subtle changes are the dangerous ones.

BACTERIOLOGIC "DISCREPANCIES"

The whole concept of variation has been developed to considerable lengths by bacteriologists. The diphtheria bacillus, for instance, being so polymorphous, so variable in virulence and at the same time so important to mankind at large, has received close attention. As shown by cultures originating from a single bacillus (Crowell [3]), it now develops that the barred forms of Westbrook can develop from solid forms and that "a real mutation has been shown by the development of a non-toxic strain"; that is, the factor of variation extends into the physiologic as well as into the morphologic realm. One learns more and more that one can never hope to really know a micro-organism, either bacterium or fungus in the fullest biologic sense until it has been followed through different environments, animal and otherwise. This statement pertains both to morphology and virulence; as is seen at present, when dealing with the several descendants of a single cell one cannot make a generalization to the effect that morphology has relation to virulence. Mellon [4] supplemented all this by saying that even bacteria are not monomorphic, but are fungi imperfecti; he described branching forms of *Bacillus coli* [5] and hinted at hybrid forms in general among the bacteria.

There is a practical result of the foregoing observations. It becomes necessary to inquire at this point whether the resistance of fungus species against heat, dyes, etc., is the same when they are freshly taken from tissue (pus, hair) as when they have been grown in the test tube for several generations. If it should develop that they are radically different, it would vitiate some of the fungistatic work in its application

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3. Crowell, M. J.: J. Bact. **11**: 65, 1926.

4. Mellon, R. R., and Jost, E. L.: Studies in Microbic Heredity III. The Hereditary Origin of Group and Specific Agglutinogens Among the Colon-Alkaligenes Organisms, J. Immunol. **11**:139 (Feb.) 1926.

5. Mellon, R. R.: Studies in Microbic Heredity I. Observations on a Primitive Form of Sexuality (Zygospore Formation) in the Colon-Typhoid Group, J. Bact. **10**:481 (Sept.) 1925.

to therapy. This threat, however, awaits actual test of the two stages of fungus micro-organisms.

BOTANICAL RESEARCHES

In the foregoing paragraphs I have drawn a somber picture. I have related some of the laboratory difficulties. I shall now turn on the promised light—or at least what I believe to be such—from the botanic field.

Comparison.—Probably the simplest use to which one can put botanic knowledge is by drawing a comparison between conditions in culture tubes and those in the grosser vegetation of gardens and elsewhere in nature. As to the latter, one is aware of the tremendous number of plant species which are closely similar in appearance and of the differences in appearance in a given species that may be occasioned simply by variations in the soil. Take wheat and rye, for instance, or the citron and the cantaloup, and particularly the various grasses and ferns. What a vast knowledge the botanist must have in order to discriminate between all these forms! In the test tubes, likewise, there are multitudes of even more closely related fungus species, and differences in the substrate will yield just as extreme differences in morphology of a fungus colony as occurs in the truck patches of the farmer. The mycologist must therefore first essay to learn his flora just as the botanist does—a tremendous task (Saccardo has catalogued more than 40,000 species), and he must also pay attention to the environment of his plants. The latter phase, involving a standard international culture medium, is receiving continued attention and need not be dilated on. To paraphrase Mellon's commentary on bacteria in relation to fungi, "Fungi may be regarded biologically as plants which have been telescoped down into a state of existence where their life cycles (and processes), although much compressed and often abbreviated, are still not obliterated."

Mutation.—Mellon,[6] a medical man, is an outstanding source of light in his "Studies in Microbic Heredity." These dealt primarily with bacteria, but also included different cultures of *Blastomyces* taken from the same patient, but from lesions at different stages of the disease. Mellon worked with monospore cultures (cultures derived from single spores) and found two different types of strains of *Blastomyces* (types I and II of Ricketts), one of which was recovered

6. Mellon, R. R.: Studies in Microbic Heredity VI: The Infective and Taxonomic Significance of a Newly Described Ascospore Stage for the Fungi of Blastomycosis, J. Bact. **11:** 229 (April) 1926; VII, Observations on the Genetic Origin of the Several Types of Fungi Found in the Lesions of Blastomycosis Hominis, ibid. **11:** 419 (June) 1926.

easily from young lesions and the other with difficulty from older ones. In the course of time, "secondary" colonies grew on the original ones; in the secondary ones, special microscopic forms (including asci) developed which were altogether different from those in the primary colony; that is, genetic changes had occurred of the same order, perhaps, as in those of Shear and Dodge which will be described later. Furthermore, the secondary colonies were so dark that they might easily be regarded as contaminants, and Mellon rightly remarked that dermatologists have not been inquiring thoroughly enough into those secondary colonies and have been jumping to conclusions after the fashion of technicians. Dermatologists must follow this up in the future.

But the outstanding accomplishment was the experimental transformation of one of these strains into the type III of Ricketts. This was accomplished simply by allowing the colonies to age (on peptone-free medium) and then by picking off the secondary colonies. Not to go into further detail, this work assigns the blastomycetic organisms to *Ascomycetes* and opens up new vistas in the understanding of the subject of virulence.

Life Cycles in Puccinia.—Yet another source of light is comparatively ancient and one which has been of tremendous economic importance to the agriculturist. The disease "red rust" [7] is referable to several races of fungi of the genus *Puccinia,* and when epidemic (epiphytic) occasions tremendous financial losses in wheat and other grains. The barberry plant was incriminated early as a reservoir of the infection. The fungus appears on it in two forms, which will be designated for short, A and B. A and B are different in that the spores are arranged in highly specialized receptacles of distinctive morphology, just as the seeds of the different flowering plants are lodged in particularly shaped flowers. These two forms are likely to be seen during the early seasons of the year on the barberry and other shrubs; later in the year other forms, C and D, will make their appearances on wheat. The D form is much more resistant to cold and has the power of wintering over and being in a position to inaugurate new infections in the spring. The morphology of the spores will be different in these different stages. Thus another example of life cycles is presented at different stages of which the organism has a different morphology; truly, it is a protean organism.

A further phase of red rust which has an important application to the medical field and which I had meant to omit from this paper because it introduced a physiologic factor, I cannot forego mentioning. Thus, in the course of the extended experiments which were necessary to

7. Stevens, F. L.: Plant Disease Fungi, New York, The Macmillan Company, 1925, p. 230. More popular account in the Encyclopaedia Britannica in discussion of "Fungi," including "bridging" species.

establish the life cycle of the red rust it was found that there were races of the fungus which were absolutely specific for certain hosts. *Puccinia graminis-tritici* will affect wheat and barley but not oats and rye; *Puccinia graminis-secalis* infects rye and barley but not wheat and oats, etc. There are yet further refinements of the situation in which there are substrains which have different actions on certain varieties of rye, wheat, etc., as the case may be, and which show how involved the premises are concerning susceptibility and immunity between fungi and host. Stakman [8] has also given much food for thought on this subject.

One may draw some comfort from these studies of the botanists because, like the dermatologists, they have made mistakes even though they had such unusual opportunities. It was not long ago that they believed that there were "bridging" hosts. Thus there was a strain of *Puccinia* which would affect one kind of grain, barley, for instance, and would not parasitize another, such as wheat. Yet after a sojourn of the barley species on some other grain, such as rye, it would have the capacity at this time of infecting the wheat which previously would not support it. This theory of "bridging hosts" has been shown to be incorrect. In this case, it was the special advantages which the botanists enjoyed in the way of experimenting with living hosts that led to the correction of the "bridging" error.

Homothallism and Heterothallism.—In 1904, Blakeslee took up the subject of homothallism and heterothallism. This meant nothing more than that in a given fungus colony which had been derived from a single spore and was consequently a "pure line" strain, the fungus cell (thallus) might have differing qualities in the sexual direction without exhibiting any morphologic evidence of this difference. It is evident that when dealing with such a phase of plant life as sexuality there should not be any question about the purity of the genesis of each plant; hence, the necessity for working only with plants developed from a single spore; pure-line or monosporous cultures as they are known.

Under these conditions it was found that if two pure-line cultures were planted adjacent to each other, the resultant colony might be entirely free from certain special and distinctive fruit bodies (perithecia or asci), whereas the combination of two other colonies which had been reared in precisely the same manner would yield colonies which produced asci. The deduction was that in the first pair cited both the members were either males or else females, while in the second example one was male and the other female. It is to be understood that all this was occurring in one and the same species, which accordingly became a heterothallic species. That is, as far as the eye and the

8. Stakman, R. C.: Racial Specialization of Parasitic Fungi, J. Staff Meetings of the Mayo Clinic, May 25, 1927, vol. 2.

microscope could reveal, all four, say, of the pure-line colonies that I have just discussed were the same; yet in one of these colonies there was the potential (sexual) capacity which, when exercised in conjunction with one of the opposite sexed ones, led to the development of fruit bodies.

The foregoing statements express the essence of the homoheterothallic situation. There is a story related to it which I shall narrate in order to crystallize the matter, and which, while not medical, has a practical economic application that may be considered in the study of medical mycologic problems.

Shear and Dodge,[9] of the Department of Agriculture in Washington, had been disturbed for a long time by almost the same kind of discrepancy that I have mentioned occurred in my cultures of *Tr. violaceum*, etc. Certain red rusts that appeared to be closely related species, growing in bakeries and on wood, showed certain vagaries in subcultures which were difficult to explain. These workers collected fifteen strains of this fungus species from red rust and finally came to suspect that the organism which had been described under no less than ten different names probably comprised only one species, or at most only a few. They were led to this belief because it so often happened that a culture which had been repeatedly subcultivated and which at first developed only conidia would eventually also show ascospores, and also because there were marked irregularities in the morphology and fruit bodies of the cultures even when they were grown from single spores. This prompted the workers to perform mating experiments in which they always employed single spore cultures from one and the same strain. It should be explained that conidia are comparatively primitive kinds of spores of a kind such as one encounters in dermatophytes (fungi imperfecti), whereas ascospores are spores of a high sexual order which often occur in specialized containers. The authors were particularly favored in their work on this fungus because the spores were so large, indeed, gigantic. They measured up to 32 microns in diameter.

The authors obtained the most striking and significant results from these matings. They found out, for instance, that ascospores were never developed in a monospore colony, that is, the progeny of a single spore—only conidia would be represented as the reproductive body. Neither were ascospores developed by planting two portions from the same monospore colony together. If, however, two different monospore colonies were planted adjacent to each other, they would sometimes produce conidia only, and at other times ascospores in addition to the conidia. By making large numbers of such double plantings (that is,

9. Shear, C. L., and Dodge, B. O.: Life Histories and Heterothallism of the Red Bread Mold Fungi of the Monilia Sitophila Group, J. Agric. Research **34**: 1019 (June 1) 1927.

all possible combinations among different monospore colonies), they were able to arrange a chart which showed that there were two categories of fungus tissue which might be, in a loose way, denominated sexual. If two sexes were planted together, nothing would develop but conidia; if unlike members were planted together, ascospores would develop. From this fact the generalization was drawn that ascospores were to be looked on as the perfect stage of the species, because they were the product of a sexual form of reproduction; on the other hand, colonies in which only conidia appeared should be regarded as imperfect phases of the life cycle of the parasite.

In other words, and viewed from a different angle, one and the same species of fungus would have different forms of fructification and therefore would be regarded as a separate species, depending on whether the species had arisen from a single spore, or whether there had been two sexually different spores present when the colony began to develop! And I fear that similar circumstances are responsible for complicating the dermatologic *Trichophyton gypseum* group. The situation is somewhat analogous to the better known one among the malarial parasites, in which the form of the parasite is so different in the asexual cycle of man and the sexual one in the mosquito.

It is not difficult to draw the lesson taught by this work of Shear and Dodge as applied to cutaneous fungi. For instance, how much greater is the difference between the two malaria cycles already cited (and also between the C and D stages of *Puccinia graminis*) than between *Coccidioides immitis* and *Blastomyces*—by comparison it is but a short step between the latter. The moral is that, as I have reiterated in the past, the way to constructive advance in medical mycology today is through attention to the fundamentals. Henceforth the species must be examined by the use of monospore cultures and not simply by sowing a large mass of fungus substance and drawing final conclusions from the results; at least a check-up must be made of the situation and colonies that have developed from single spores must be studied in the same way that Shear and Dodge studied them. It should be determined whether heterothallism and homothallism also occur in dermatophytes.

To illustrate concretely, during the last eight years I have been able to collect seven strains of fungi causing blastomycosis. In addition to these, two others were submitted from widely different sources which purported to be valid. Both of these turned out to be *Pencillium brevicaule*. It is inconceivable that there could be any explanation for this coincidence except that it was due to definite biologic laws working alike on the two strains. I strongly suspect that the original cultures were of the Gilchrist type, but that they had advanced to a higher, penicillial form as the result of altered environment incident to repeated subculture; whether heterothallism figures in the matter remains to be determined.

The light which these studies throw on other difficulties and discrepancies mentioned in the first part of this paper is clear. For instance, the difficulty with the hanging drops might have been due to the kind of mycelium, homothallic or heterothallic, used in transplanting.

Prior to the discovery of the sexual phase in fungi, I felt safe from this disturbing factor. I had understood that the concept of mutation applied only to those forms of life which were subject to Mendel's law. But, as shown by the work of Shear and Dodge, there remains the possibility of hybridization, albeit a much lower grade than usually conceived, and perhaps not quite within the definition. It may be imagined at once what this would mean to dermatologists; such factors as atavism, dominance, recessiveness, etc., may explain many of the irregularities of clinical mycology as well as the irregular results of which I complained earlier in the paper.

SUMMARY

The botanists have been much more fortunate than their medical confrères in having an abundance of material to work with and in so frequently having unlimited living hosts on which to experiment and reproduce the disease under study. They have been able, thus, to outstrip dermatologists in many phases of micro-organismal work, just as dermatologists have outstripped them in developing some of the serologic and other biochemical phenomena of life. They have taught many lessons: first, that there are almost undreamed of possibilities in the way of morphologic variation among some species of fungi, and that in order to determine whether homothallism and heterothallism also obtain to any notable extent among the dermatophytes one must employ the monospore technic; second, that one must not place too rigid an interpretation on morphology in its relation to species determination; third, that there are even possibilities of mutation occurring here.

A further lesson brought home is that one must know the complete life cycle of a fungus parasite before one can ever hope to attack it from the logical and effective hygienic standpoint; that is, its habitat, if there is any, in nature. Thus, under such a differing environment as human tissues on the one hand and vegetation on the other, it is natural to expect that a given species woud appear entirely different. Even in vegetation the appearances might be different at different seasons of the year or under other circumstances, as has been learned from the red rust of wheat.

In spite of the general air of pessimism that has pervaded this paper, there is a great deal to be thankful for. Within certain limits parasitic fungi maintain a fairly uniform appearance as they parasitize animal tissue. Furthermore, after having become stabilized in such a

more or less prolonged habitat, they yield, fortunately, a fairly consistent morphology in the initial cultures. These expressions of fungus activity are the ones which are most important to the physician, and are the ones that immediately concern his patient. Indeed, my purpose in this paper is not to discourage prospective or other mycologists; much is still possible.

I realize that I have not reported new facts or other advances in science, but it is as necessary to collate facts as to establish them. It is necessary in all lines of endeavor to pause from time to time and take an inventory of one's position. I have attempted this in relation to one phase of fungus activity; that is, variation. I have further attempted to caution against the development of a sense of smugness, and have endeavored to enlarge the vision of fungus capacities, to indicate a line of investigation that dermatologists can embark on other than those which Sabouraud exhausted many years ago. Finally, as expressed at the beginning of the paper, I have tried to indicate to the medical profession at large that the path of the mycologist is not one of roses.

THE THERAPEUTIC ACTION OF COLLOIDAL MERCURY SULPHIDE (HILLE) AND OF OTHER COLLOIDAL HEAVY METAL SULPHIDES IN SYPHILIS EXPERIMENTALLY PRODUCED IN RABBITS*

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There are few reports in the literature of investigations on the therapeutic properties of colloidal solutions of the heavy metals or their salts in syphilis experimentally produced. Neisser[1] studied the therapeutic activities of colloidal mercury and other colloidal heavy metals in syphilis experimentally produced in monkeys. Evers and Albrecht[2] employed a preparation of bismuth and arsenic adsorbed on an organic colloidal complex and also a colloidal solution of bismuth, arsenious acid and gum arabic in the treatment of rabbits in which syphilis had been experimentally produced, and obtained favorable results. Iwasa[3] reported encouraging observations with glutin-copper in rabbits experimentally infected with syphilis.

In this communication, the results obtained from the study of the therapeutic activity of colloidal mercury sulphide (HgS), colloidal bismuth sulphide (Bi2S3), colloidal bismuth sulpharsenite (BiAsS3), colloidal copper sulphide (CuS), colloidal copper sulpharsenite (Cu3As2S6) and mervenol (colloidal mercury sulphide and colloidal copper sulphide in equimolecular proportions) in syphilis experimentally brought about in the rabbit are presented.[4]

PROCEDURE

The colloids studied were prepared by the condensation method. The colloidal heavy metal salts were each stabilized by a hydrolized protein solution. They were physiologically isotonic and possessed a slight, pleasant, bland taste. The colloidal solutions were stable for the twenty-month period of their retention in the laboratory. They were entirely suited for intravenous, intramuscular and peroral

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* From the Department of Physiology of the University of Chicago.

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1. Neisser, A.: Arb. a. d. k. Gsndhtsamte. **37**:227, 1911.

2. Evers, E., and Albrecht, B.: Deutsche med. Wchnschr. **51**:1654, 1925.

3. Iwasa, D.: Deutsche med. Wchnschr. **52**:321, 1926.

4. The colloidal solutions used were prepared and supplied by Dr. Hermann Hille, Chicago. Analyses of the solutions of colloidal mercury sulphide and of colloidal bismuth sulphide by the Department of Chemistry, University of Chicago, confirmed their metallic content.

administration. The maximum tolerated and minimum lethal doses of the colloids administered to rabbits were recently reported.[5]

The method employed in this investigation was essentially that previously described.[6] The Nichols strain of *Spirochaeta pallida* was inoculated into the right testis of the rabbit. During the eighth week of the disease, when the testicular and scrotal lesions were well marked but still progressive and the Wassermann[7] and Kahn[7] reactions of the blood were positive, the animals were divided into two groups—those that received treatment and those that were used as controls. The therapeutic regimens instituted varied with the different colloids.

In view of the opinion voiced by Kolmer[8] that repeated small doses of mercurials are required to bring about curative effects in syphilis produced in rabbits, treatments with colloidal mercury sulphide, colloidal copper sulphide and mervenol each consisted of twelve intravenous injections at semiweekly intervals. One fifteenth of the maximum tolerated dose was employed for the first four treatments and one tenth of the dosis tolerata for the remainder.

Since arsenic and bismuth are more actively spirocheticidal than mercury and copper, four weekly intravenous injections of colloidal copper sulpharsenite, each one fourth of its maximum tolerated dose, and three weekly intravenous injections of colloidal bismuth sulphide, one of one fourth and two of one half of the dosis tolerata, were given. One group of actively syphilitic rabbits was given twelve semi-weekly intravenous injections of 3 cc. per kilogram of body weight of a 7 per cent solution of the protective proteins employed in the preparation of the colloidal heavy metal salts. The protective colloid solution was used in twice the concentration and in approximately three times the quantity of the stabilizing menstrua in the colloidal heavy metal salt therapies. Semiweekly or weekly observations of the syphilitic lesions and weekly or biweekly Wassermann and Kahn reactions of the blood were made to determine the healing powers of the various colloids.

The sterilizing powers of the drugs were determined in three ways: 1. The rabbits treated with colloidal mercury sulphide, colloidal bismuth sulphide, colloidal copper sulpharsenite and the protective colloid solution, as well as the corresponding control animals were observed for a period of at least four months after the healing of the testicular and scrotal lesions and reversal of the positive Wassermann and Kahn reactions of the blood for the appearance of relapses of active syphilis. As is well known, the clinical and serologic signs of syphilis eventually disappear spontaneously in the untreated rabbit, although the animal continues to harbor *Spirochaeta pallida*. 2. At the end of this four-month period, lymph nodes were transferred from those animals which did not develop recrudescences of active syphilis in order to determine whether or not they were sterilized of the spirochete. The rabbits to which the transfers were made were observed for four months for the appearance of clinical or serologic signs of syphilis. 3. Since the prophylactic and sterilizing powers of a series of organic arsenicals and mercurials were found practically to parallel each other,[9] the effectiveness of the maximum

5. Wakerlin, G. E., and Eiseman, C.: Am. J. Syph. **12**:384, 1928.

6. Wakerlin, G. E.; Loevenhart, A. S., and Lorenz, W. F.: J. Pharmacol. & Exper. Therap. **26**:187 (Oct.) 1925.

7. All of the Wassermann reactions reported were performed at the Wisconsin Psychiatric Institute, Madison, Wis. The Kahn reactions were performed by Dr. O. H. Horrall of the Department of Physiology, University of Chicago.

8. Kolmer, J. A.: Principles and Practice of Chemotherapy, Philadelphia, W. B. Saunders Company, 1926, p. 330.

9. Wakerlin, G. E., and Loevenhart, A. S.: J. Pharmacol. & Exper. Therap. **34**:15 (Sept.) 1928.

tolerated doses of colloidal mercury sulphide and of colloidal bismuth sulpharsenite, administered intravenously as prophylactics twenty-four hours after the unilateral intratesticular inoculation of *Spirochaeta pallida,* was determined. The rabbits so treated were observed for the development of clinical and serologic signs of syphilis during a subsequent period of six months.

RESULTS

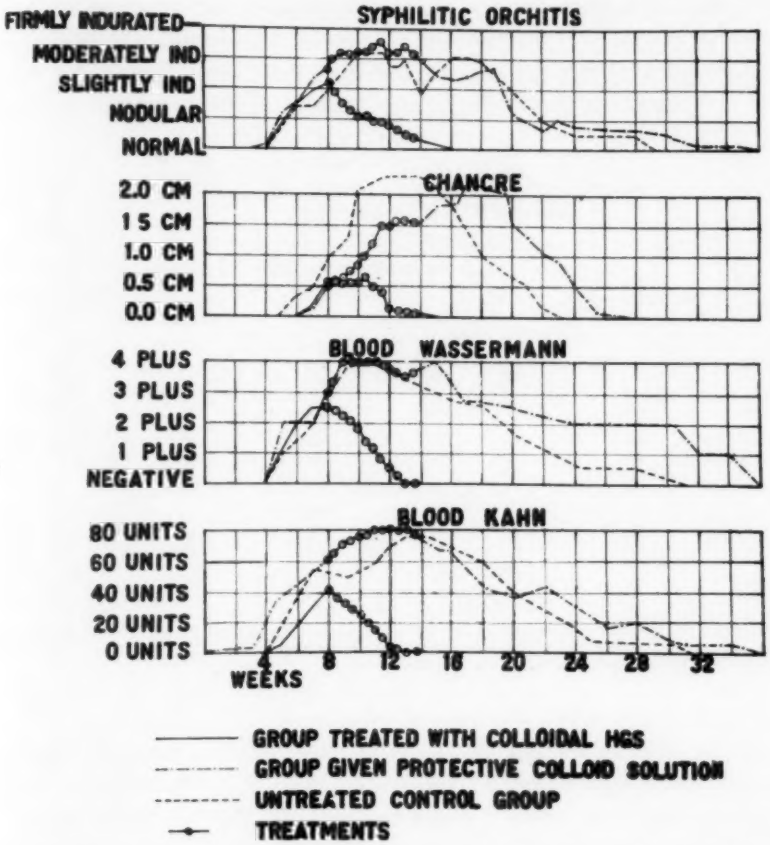
Colloidal Mercury Sulphide (Hille).—The maximum tolerated and minimum lethal doses of colloidal mercury sulphide for intravenous injection into rabbits are 30 and 40 mg. per kilogram of body weight, respectively. The drug contains 86.21 per cent of metallic mercury by weight. Four rabbits treated with this colloid evidenced a prompt and rapid healing of the orchitis and descent of the positiveness of the Wassermann and Kahn reactions of the blood, whereas the three control animals showed pronounced local lesions and strongly positive serologic conditions of long duration. The first four injections of one fifteenth of the maximum tolerated dose of colloidal mercury sulphide prevented further development of the chancres, and an increase to one tenth of the dosis tolerata resulted in a prompt healing of the scrotal lesions. The results are shown graphically in the accompanying chart. The areas between the curves of the chart for the group treated with colloidal mercury sulphide, and the practically parallel curves for the control group and for the group injected with the protective colloid solution, represent the healing power of the colloidal heavy metal salt.

The average durations, from the beginning of treatment, of the orchitis, chancre and positive Wassermann and Kahn reactions of the blood of the four rabbits treated with colloidal mercury sulphide were twenty-nine, twenty-one, twenty-four and twenty-eight days, respectively. The corresponding figures for the untreated controls were 110, 83, 120 and 125 days. The data for the individual animals are shown in table 1. Treatment with colloidal mercury sulphide, therefore, reduced the average durations of these four criteria of drug healing power by 83, 75, 78 and 78 per cent.

None of the four rabbits treated with colloidal mercury sulphide developed relapses of active syphilis during the observation period of four months subsequent to the healing of the local lesions and the reversal of the positive serologic observations. On the other hand, two of the three control animals developed generalized lesions during and subsequent to the healing of the orchitis and chancre.

The transfer of lymph nodes made from the four rabbits treated with colloidal mercury sulphide gave negative results for *Spirochaeta pallida.* A transfer from the one control which did not have a relapse was, of course, positive.

The intravenous administration of the maximum tolerated dose of colloidal mercury sulphide twenty-four hours after the intratesticular inoculation of *Spirochaeta pallida* afforded complete protection against the development of syphilis in two of three rabbits. A confirmatory lymph node transfer from one of these animals gave a negative result for the spirochete at the end of the six months' observation period. The third rabbit, however, developed an orchitis, a positive Wassermann



The healing power of colloidal mercury sulphide in syphilis experimentally produced in rabbits.

reaction of the blood and a positive reaction to the Kahn test at the beginning of the fourth month subsequent to intratesticular inoculation. Seventeen rabbits simultaneously inoculated with *Spirochaeta pallida* but not treated prophylactically all developed active syphilis in from four to five weeks.

Preliminary experimentation indicates that colloidal mercury sulphide possesses an as yet indeterminate antisyphilitic power when

administered perorally. A report of this feature will be rendered subsequent to a more extensive investigation.

Colloidal Bismuth Sulphide (Hille).—Colloidal bismuth sulphide possesses maximum tolerated and minimum lethal doses of 40 and 60 mg. per kilogram for rabbits given intravenous injections. The first treatment of 10 mg. of colloidal bismuth sulphide per kilogram initiated a resolution of the orchitis but did not reduce materially the positiveness of the Wassermann tests on the blood nor impede the progress of the chancres and positive Kahn titers of five actively syphilitic rabbits. The second and third treatments of 20 mg. per kilogram, however, proved effective in their action on these four criteria of drug healing power. Indeed, the average durations of the orchitis, chancre and positive Was-

TABLE 1.—*The Healing Power of Colloidal Mercury Sulphide in Syphilis Experimentally Produced in the Rabbit*

Rabbit Number	Durations From the Beginning of Treatment, in Days			
	Orchitis	Chancre	Positive Wassermann	Positive Kahn
Treated Group*				
23	14	0	7	21
27	56	49	34	34
32	35	35	35	35
37	11	0	21	21
Totals	116	84	97	111
Averages	29	21	24	28
Control Group†				
30	147	105	161	161
33	90	70	96	103
39	94	73	103	110
Totals	331	248	360	374
Averages	110	83	120	125

* The treated group received a total of twelve semiweekly intravenous injections of colloidal mercury sulphide, four of 2 mg. per kilogram and eight of 3 mg. per kilogram.
† The control group did not receive treatment.

sermann and Kahn reactions of the blood from the beginning of the treatment of the five rabbits given colloidal bismuth sulphide were seventeen, fourteen, twelve and nineteen days, respectively, as compared with seventy-two, forty-three, seventy and fifty-five days for the five untreated controls. The data for the individual rabbits are shown in table 2. Treatment with colloidal bismuth sulphide, therefore, shortened the average duration of these four factors by 76, 67, 83 and 65 per cent.

Each of the five rabbits treated with colloidal bismuth sulphide developed relapses of active syphilis from one and one-half to three months subsequent to the complete healing of the local lesions and reversal of the positive Wassermann and Kahn reactions of the blood. Three of the five control animals showed generalized lesions of syphilis. The transfer of lymph nodes from the remaining two untreated rabbits gave a positive result for *Spirochaeta pallida.*

Colloidal Bismuth Sulpharsenite (Hille).—Colloidal bismuth sulpharsenite has a maximum tolerated dose of 5 mg. per kilogram and a minimum lethal dose of 10 mg. per kilogram when given intravenously to rabbits. An attempt to abort the development of syphilis in two rabbits by the administration of the dosis tolerata of colloidal bismuth sulpharsenite, twenty-four hours after intratesticular inoculation with *Spirochaeta pallida,* was unsuccessful. The animals so treated evidenced clinical and serologic signs of syphilis simultaneously with the untreated controls.

Colloidal Copper Sulphide (Hille).—The maximum tolerated and minimum lethal doses of colloidal copper sulphide when injected intra-

TABLE 2.—*The Healing Power of Colloidal Bismuth Sulphide in Syphilis Experimentally Produced in the Rabbit*

Rabbit Number	Durations From the Beginning of Treatment, in Days			
	Orchitis	Chancre	Positive Wassermann	Positive Kahn
	Treated Group*			
7	14	0	0	20
10	14	14	13	13
11	27	27	13	34
17	14	14	13	13
18	14	14	20	13
Totals	83	69	59	93
Averages	17	14	12	19
	Control Group†			
5	83	93	78	84
8	92	41	49	49
9	69	0	104	34
16	75	68	48	61
19	42	14	71	49
Totals	361	216	350	277
Averages	72	43	70	55

* The treated group received a total of three weekly intravenous injections of colloidal bismuth sulphide, one of 10 mg. per kilogram and two of 20 mg. per kilogram.
† The control group did not receive treatment.

venously into rabbits are 10 and 20 mg. per kilogram. The clinical and serologic course of three actively syphilitic rabbits given twelve semiweekly intravenous injections of colloidal copper sulphide, four of one fifteenth and eight of one tenth of the maximum tolerated dose, practically paralleled the clinical and serologic course of the three corresponding control animals. As seen from table 3, the average durations from the beginning of treatment of the orchitis, chancre and positive Wassermann and Kahn tests of the blood were eighty-two, twenty-four, seventy-one and seventy-two days for the treated group and seventy, thirty-six, seventy-four and ninety-three days for the control group.

Colloidal Copper Sulpharsenite (Hille).—The critical toxicologic figures for colloidal copper sulpharsenite are 30 and 40 mg. per kilogram. Four weekly intravenous injections of one-fourth of the maxi-

mum tolerated dose of this colloid partially inhibited the progressive character of the orchitis and chancres of the three treated rabbits and induced a somewhat more rapid involution of these lesions than occurred in the three control animals. The serologic behavior of the rabbits given colloidal copper sulpharsenite, however, practically paralleled that of the controls. As is shown in table 4, the average durations of the orchitis, chancre and positive Wassermann and Kahn reactions of the blood, from the inception of therapeusis, were eighty-eight, forty-three, one hundred and thirty-six, and one hundred and thirty-one days for the treated group, and one hundred and ten, eighty-three, one hundred and twenty, and one hundred and twenty-five days for the control group. The duration of the four criteria of drug healing power were therefore

TABLE 3.—*The Healing Power of Colloidal Copper Sulphide in Syphilis Experimentally Produced in the Rabbit*

Rabbit Number	Durations From the Beginning of Treatment, in Days			
	Orchitis	Chancre	Positive Wassermann	Positive Kahn
	Treated Group*			
44	111	0	111	111
48	69	52	69	52
49	65	21	34	52
Totals	245	73	214	215
Averages	82	24	71	72
	Control Group†			
51	76	0	83	97
54	52	0	69	83
59	83	107	69	100
Totals	211	107	221	280
Averages	70	36	74	93

* The treated group received a total of twelve semiweekly intravenous injections of colloidal copper sulphide, four of 0.7 mg. per kilogram and eight of 1 mg. per kilogram.
† The control group did not receive treatment.

reduced by treatment with colloidal copper sulpharsenite 20, 48, 0 and 0 per cent, respectively.

During the observation period of four months following the healing of the local lesions and reversal of the positive serologic observations, two of the three rabbits treated with colloidal copper sulpharsenite developed generalized syphilitic lesions, as did also two of the three control animals. The remaining two rabbits both gave positive results following the transfer of lymph nodes.

Mervenol.—The dosis tolerata and dosis lethalis of mervenol (colloidal mercury sulphide and colloidal copper sulphide) by vein are 20 and 30 mg. per kilogram for rabbits.

The first four semiweekly treatments of one fifteenth of the maximum tolerated dose of mervenol produced a fairly rapid descent of the orchitis of three actively syphilitic rabbits, but only partially inhibited the growth of the chancre. The following eight semiweekly injections

of one tenth of the maximum tolerated dose of mervenol, however, caused a rapid healing of the orchitis and chancre. The positive Wassermann and Kahn reactions of the blood were likewise more or less uninfluenced by the first four treatments, although the following eight injections hastened somewhat the descent of these to negative. The average durations of the orchitis, chancre and positive Wassermann and Kahn reactions of the blood from the beginning of the treatment were twenty-one, ten, sixty-three, and sixty-three days for the treated group of three animals, and seventy, thirty-six, seventy-four and ninety-three days for the control group of three animals (table 5). The percentages of reduction of these four factors by treatment with mervenol were therefore 70, 72, 15 and 32 per cent, respectively.

TABLE 4.—*The Healing Power of Colloidal Copper Sulpharsenite in Syphilis Experimentally Produced in the Rabbit*

Rabbit Number	Durations From the Beginning of Treatment, in Days			
	Orchitis	Chancre	Positive Wassermann	Positive Kahn
	Treated Group*			
28	96	40	217	200
35	78	0	96	96
38	89	89	90	96
Totals	263	129	400	392
Averages	88	43	136	131
	Control Group†			
30	147	105	161	161
33	90	70	96	103
39	94	73	103	110
Totals	331	248	360	374
Averages	110	83	120	125

* The treated group received a total of four weekly intravenous injections of colloidal copper sulpharsenite, each of 7.5 mg. per kilogram.
† The control group did not receive treatment.

Protective Colloid Solution.—The stabilizing menstruum employed in the preparation of the heavy metal colloids was without discernible toxicologic effects on rabbits in the maximum dosage used—20 cc. per kilogram injected intravenously.[5] The clinical and serologic courses of the three rabbits with active syphilis given twelve intravenous injections of 3 cc. of the protective colloid solution per kilogram at semiweekly intervals were practically parallel with the clinical and serologic involvements of the three untreated control animals (chart 1). The durations of the orchitis, chancre and positive Wassermann and Kahn reactions of the blood from the inception of treatment were somewhat longer for the group given the protective colloid solution than for the untreated control group. As detailed in table 6, the durations for the former were one hundred and fifty-three, ninety-seven, one hundred and fifty-nine, and one hundred and fifty-nine days, and for the latter, one hundred and ten, eighty-three, one hundred twenty, and one hundred twenty-five days.

During the four months subsequent to the healing of the local lesions and reversal of the positive serologic observations, each of the three animals given protective colloid and two of the three untreated controls developed generalized lesions of syphilis.

TABLE 5.—*The Healing Power of Mervenol (Colloidal Mercury Sulphide and Colloidal Copper Sulphide) in Syphilis Experimentally Produced in the Rabbit*

Rabbit Number	Durations From the Beginning of Treatment, in Days			
	Orchitis	Chancre	Positive Wassermann	Positive Kahn
Treated Group*				
42	31	31	52	52
53	16	0	69	69
58	16	0	69	69
Totals	63	31	190	190
Averages	21	10	63	63
Control Group†				
51	76	0	83	97
54	52	0	69	83
59	83	107	69	100
Totals	211	107	221	280
Averages	70	36	74	93

* The treated group received a total of twelve semiweekly intravenous injections of mervenol, four of 1.3 mg. per kilogram and eight of 2 mg. per kilogram.
† The control group did not receive treatment.

TABLE 6.—*The Healing Power of the Protective Colloid Solution in Syphilis Experimentally Produced in the Rabbit*

Rabbit Number	Durations From the Beginning of Treatment, in Days			
	Orchitis	Chancre	Positive Wassermann	Positive Kahn
Treated Group*				
25	103	65	113	113
26	161	134	168	168
29	196	91	196	196
Totals	460	290	477	477
Averages	153	97	159	159
Control Group†				
30	147	105	161	161
33	90	70	96	103
39	94	73	103	110
Totals	331	248	360	374
Averages	110	83	120	125

* The treated group received a total of twelve semiweekly intravenous injections of 7 per cent protective colloid solution in a dosage of 3 cc. per kilogram.
† The control group did not receive treatment.

None of the approximately 150 intravenous injections of the colloidal heavy metal salts given in this investigation produced any objective signs of irritation at the site of administration. In no instance was there any objective manifestation of anaphylaxis. The repeated administration of the colloids did not cause discernible toxic symptoms

in the animals. The rabbits given injections of colloidal mercury sulphide presented a notably excellent physical appearance subsequent to the period of treatment.

COMMENT

The results demonstrate conclusively that colloidal mercury sulphide administered as previously outlined is an excellent healing agent in syphilis produced experimentally in rabbits. In all of the four criteria of drug healing efficacy, namely, orchitis, chancre and positive Wassermann and positive Kahn reactions of the blood, the response to the action of the colloidal heavy metal salt was favorable and rapid. The percentages of reduction of the average durations of the orchitis, chancre and positive Wassermann reaction of the blood obtained by treatment with colloidal mercury sulphide, as previously stated, were 83, 75 and 78. The corresponding figures previously determined for intravenous injections of neoarsphenamine were 57, 67 and 67 per cent; for intramuscular injections of mercuric salicylate, 34, 41 and 60,[10] and for intravenous injections of flumerin, 42, 60 and 75.[10] Neoarsphenamine and mercuric salicylate were administered in three weekly injections, the former one fourth and the latter one third of the respective maximum tolerated doses. Four weekly injections of flumerin were used, two of one quarter and two of one half of the dosis tolerata. White, Hill, Moore and Young[11] found that twelve daily intravenous injections of one tenth of the maximum tolerated dose of flumerin caused a resolution of the lesions in two syphilitic rabbits and a persistence in three others, whereas ten daily treatments of one sixth of the maximum tolerated dose of flumerin produced a resolution of the lesions in each of five rabbits.

Because of the differences in the regimens of treatment, as well as other factors, a comparison of neoarsphenamine, mercuric salicylate and flumerin with colloidal mercury sulphide can be only approximate, but the results are nevertheless demonstrative of the powerful healing properties of this colloid in syphilis produced experimentally in the rabbit. The results of this investigation are in accord with the favorable observations made by Paterson and reported by Hille[12] for colloidal mercury sulphide therapy in Wassermann-fast syphilis in man.

The results also demonstrate that colloidal mercury sulphide is a more powerful sterilizing agent in syphilis experimentally produced in rabbits than any of the other mercurials heretofore investigated.

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10. Wakerlin, G. E., and Loevenhart, A. S.: Unpublished data.

11. White, E. C.; Hill, J. H.; Moore, J. E., and Young, H. H.: Flumerin—A New Mercurial for the Intravenous Treatment of Syphilis, J. A. M. A. **79**:877 (Sept. 9) 1922.

12. Hille, H.: Clin. Med. & Surg. **34**:28, 1927.

Thus, all four of the rabbits treated with colloidal mercury sulphide were sterilized of *Spirochaeta pallida* as subsequent to treatment they did not show relapses of active syphilis and gave negative results following the transfer of lymph nodes. On the other hand, Young and his associates [11] reported that twelve daily intravenous injections of one tenth of the maximum tolerated dose of flumerin sterilized only one of five syphilitic rabbits, although Hill and Young [13] found that seven of eight other animals were sterilized by from ten to fifteen daily treatments of one sixth of the dosis tolerata of flumerin. Gruhzit [14] found that twelve intravenous injections of approximately one sixth of the maximum tolerated dose of mercurosal, given at from two to three day intervals, sterilized only four of six syphilitic rabbits. Furthermore, the maximum tolerated dose of colloidal mercury sulphide was effective as a prophylactic or abortive in two or three rabbits. In the third animal, the drug delayed the development of signs of syphilis for approximately two months. On the other hand, the maximum tolerated dose of neither flumerin nor mercuric salicylate afforded any protection against the development of syphilis produced in rabbits by the same technic.[9] The animals so treated showed signs of syphilis simultaneously with the untreated controls. The results reported for colloidal mercury sulphide therapy in rabbits in which syphilis had been produced experimentally cannot, of course, be extended to include other colloidal mercury preparations without additional experimental work, since it is known that the same chemical substance in colloidal form, when prepared by different methods, may show wide variations in toxicologic and therapeutic properties.

The results show that colloidal bismuth sulphide in the range of one half of its maximum tolerated dose is an efficacious healing agent in rabbits experimentally infected with syphilis, but that one fourth of its tolerated dose is less effective. Reports in the literature indicate that about one third of the tolerated doses of sodium potassium bismuth tartrate and of potassium bismuth tartrate proved effective in healing the lesions of syphilitic rabbits. That colloidal bismuth sulphide is inferior as an antisyphilitic to potassium bismuth tartrate is further attested by the inability of the former to sterilize any of the five rabbits treated with it, whereas Raiziss and Severac [15] found that somewhat less than one third of the maximum tolerated dose of the latter injected intramuscularly sterilized two syphilitic rabbits.

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13. Hill, J. H., and Young, H. H.: Experimental Studies with Mercurial in Experimental Syphilis, J. A. M. A. **80**:1365 (May 12) 1923.

14. Gruhzit, O. M. Mercurosal in Experimental Rabbit Syphilis, Arch. Dermat. & Syph. **11**:509 (April) 1925.

15. Raiziss, G., and Severac, M.: Curative Effect of Bismuth Compounds in Experimental Rabbit Syphilis, Arch. Dermat. & Syph. **12**:661 (Nov.) 1925.

Colloidal bismuth sulpharsenite, despite the theoretical advantages of its combined bismuth and arsenic content, possesses low spirocheticidal power, as its maximum tolerated dose does not afford protection against the development of syphilis produced experimentally in the rabbit.

The observations with colloidal copper sulphide and colloidal copper sulpharsenite make evident that the former is devoid of antisyphilitic properties and that the modest antisyphilitic action of the latter is therefore probably due to its arsenic radicle. The negative results with copper are in accord with the observations of Neisser [1] and Levaditi,[16] although perhaps at variance with those of Iwasa.[3]

In the range of one tenth of its maximum tolerated dose, mervenol (colloidal mercury sulphide and colloidal copper sulphide in equimolecular proportions) exerts an effective healing action on the orchitis and chancres of rabbits infected experimentally with syphilis, although the simultaneous effect of the drug on the serologic conditions is considerably less. Mervenol, therefore, is inferior to colloidal mercury sulphide as an antisyphilitic agent. The percentages of reduction in the durations of the four criteria of healing power for the former drug were about 60 per cent of the corresponding percentages for the latter. Undoubtedly, this difference is accounted for by the fact that approximately 30 per cent of mervenol by weight is composed of colloidal copper sulphide, which is devoid of antisyphilitic action and is approximately twice as toxic as the other component, colloidal mercury sulphide. Since the maximum tolerated dose of mervenol is 20 mg. per kilogram, the first four treatments of one fifteenth of its maximum tolerated dose and the remaining eight injections of one tenth of its maximum tolerated dose were equivalent to dosages of 0.9 and 1.4 mg. of colloidal mercury sulphide per kilogram of body weight, respectively. Both the dosage and the therapeutic effect of the colloidal mercury sulphide administered as mervenol were in consequence approximately one half of the dosage and antisyphilitic action of colloidal mercury sulphide administered as such. Colloidal mercury sulphide, therefore, possesses healing action in syphilis experimentally produced in rabbits even when the amounts used are as small as one twentieth and one thirtieth of the maximum tolerated dose.

The failure of the protective colloid solution to exert any effect on the clinical and serologic course of syphilis produced experimentally in the rabbit demonstrates the residence of the antisyphilitic potency of colloidal mercury sulphide in the heavy metal salt itself.

The absence of irritant effects on the tissues at the site of intravenous injection, as well as the absence of allergic phenomena during

16. Levaditi, C.: Compt. rend. Soc. de biol. **97**:167 (April) 1927.

the course of treatment, makes evident the suitableness of these colloids for intravenous use.

Of the five colloidal heavy metal sulphides studied, therefore, colloidal mercury sulphide, because of its low toxicity and its effective healing action and definite sterilizing properties in rabbits experimentally infected with syphilis, should be accorded a thorough investigation in the therapy of syphilis in man.

SUMMARY

1. Colloidal mercury sulphide (Hille), in the dosages employed, possesses excellent healing and definite sterilizing properties in the rabbit experimentally infected with syphilis. The potency of colloidal mercury sulphide (Hille) in syphilis experimentally produced in the rabbit is superior to that of other known mercurials.

2. Colloidal bismuth sulphide (Hille), in a range of one half of its maximum tolerated dose, is an effective healing agent but an ineffectual sterilizing agent in actively syphilitic rabbits. As an antisyphilitic agent, colloidal bismuth sulphide (Hille) is inferior to potassium bismuth tartrate.

3. The maximum tolerated dose of colloidal bismuth sulpharsenite (Hille) is without effect in the prophylaxis of syphilis produced in the rabbit.

4. Colloidal copper sulphide (Hille), in the dosages cited, is devoid of therapeutic activity in actively syphilitic rabbits.

5. Colloidal copper sulpharsenite (Hille), in the amounts employed, possesses a slight healing action but no sterilizing activity in syphilitic rabbits.

6. The therapeutic activity of mervenol in syphilis experimentally produced in the rabbit probably resides wholly in its colloidal mercury sulphide (Hille) component.

7. The protective colloid solution employed to stabilize the colloidal heavy metal salts is entirely without antisyphilitic properties for rabbits.

8. All of the colloids investigated are without deleterious effects on the tissues at the site of intravenous administration and are apparently free from properties responsible for the production of anaphylaxis in rabbits.

9. Because of its low toxicity and its effective healing action and definite sterilizing properties in rabbits experimentally infected with syphilis, colloidal mercury sulphide (Hille) should receive an adequate experimental study in the therapeusis of syphilis in man.

RETENTION OF BISMUTH IN THE ORGANISM IN THE TREATMENT OF SYPHILIS*

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One of the most outstanding characteristics in the treatment of syphilitic patients with bismuth, as with mercury, is that the metal is excreted rather slowly by the body. Thus, for a long time after the treatment is finished, a considerable amount of the metal remains in the body, maintaining an antisyphilitic effect.

In dealing with the retention of bismuth, a clear distinction should be made between totally differing conditions:

Deposits of bismuth remain at the site of intramuscular and subcutaneous injection, and are gradually absorbed at a varying rate, thus maintaining an intensive antisyphilitic effect. Numerous investigations, chemical as well as radioscopic, have shown that such deposits may contain large quantities of bismuth, especially if bismuth compounds of low solubility, suspended in mineral or vegetable oils, have been used, thus delaying the absorption considerably. Under these conditions, deposits of bismuth may remain unabsorbed for a long time, even years, probably because they are gradually becoming encapsulated by the surrounding tissue. For this reason, it has been possible in many cases to inject considerably larger, even very large, doses of these preparations without causing the well known symptoms of intoxication. There are, in this respect, substantial differences between the various bismuth compounds—differences which depend largely on their chemical formulas and on the fineness of the suspended particles of these compounds. These are the two main factors which determine the rate of absorption. A considerable literature dealing with the rate of absorption of different bismuth compounds is already available, and reference to this should prove sufficient.[1]

Differing from the foregoing type, or "quasi-retention," is what I would call the "true retention" of bismuth, or "bismuth remanens, sensu strictiori," by which is meant the diffuse storage of bismuth in all tissues of the body, common in all treatment in which this metal is employed, even in intravenous injections, though with this form there is rapid excretion.

This storage decreases just as soon as the introduction of the bismuth is discontinued or the dosage reduced, and the concentration of bismuth

* Submitted for publication, Aug. 6, 1928.

1. Handb. d. Haut. u. Geschlechtskr. **18**:319, 1928.

in the blood becomes less. This is proved by the fact that bismuth is excreted continuously, even when no more has been given; this excretion may continue for a long time, even for months, a condition which is better known, and has been more thoroughly studied, in the case of treatment with mercury, which drug is not administered exclusively by injection, as is bismuth. There is no doubt that this saturation of the tissues with bismuth is of some therapeutic importance, not only because of its effect on the spirochete, but also because the continuance of this saturation makes it possible to maintain a certain antisyphilitic effect for some time after the cessation of treatment. The liberation of bismuth from the tissues keeps up a certain concentration of bismuth in the blood, which gradually decreases as the metal is excreted. Only the bismuth which is deposited in the organs of excretion, especially in the kidneys, liver and intestines, is subject to other conditions, being excreted—at least partially—without passing through the blood stream.

Numerous investigations have proved that the distribution of bismuth in the body is irregular. The more important investigations were made by Akamatzu,[2] Lomholt,[3] Levy and Selter,[4] Biro Istvan,[5] Levaditi, Girard and Manin [6] and Gruhzit, Tendick and Sultzaberger.[7] In some organs, the concentration of bismuth is high, in others low, but the reciprocal quantity ratios between the various organs are relatively constant, irrespective of which preparation of bismuth has been used, and whether the investigation is made at an early or a later date during the treatment. There are, of course, certain disagreements among the results obtained by the various investigators, but, on the whole, they agree fairly well.

In judging therapeutic effect, the differences in distribution are not so important as the maximum quantities of bismuth which can be deposited in this way without causing any poisoning.

For practical reasons, exact investigations of this kind can be made only on animals. In human beings, it is possible to investigate the excretion in the urine and feces during a certain period, and to compare the quantity found to the quantity injected, but it is impossible to know

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2. Akamatzu, M.: Acta scholae med. univ. imp. Kioto **4**:295, 1921-1922.

3. Christiansen, Hevesy and Lomholt: Compt. rend. Acad. d. sc. **178**:1324, 1924. Lomholt, S.: Biochem. J. **18**:693, 1924; Ugesk. f. Læger **87**:141, 186 and 225, 1925; Handb. d. Haut. u. Geschlechtskr. **18**:267, 1928.

4. Levy and Selter: Arch. f. Kinderh. **75**:241 and 281, 1925.

5. Istvan, Biro: Magyar Orvosi Arch **26**:335, 1925.

6. Levaditi, Nicolau, Schoen, Girard and Manin: Ann. de l'Inst. Pasteur **60**:541, 1926.

7. Gruhzit, Tendick and Sultzaberger: Am. J. Syph. **11**:87 and 103, 1927.

definitely how much of the missing quantity is left at the site of injection, and how much is still diffused and stored in the various organs and tissues.

The most rational method of investigation on animals is to estimate definitely the quantity of bismuth contained in the various organs and tissues of the animal after a certain amount of treatment is given. This, however, is difficult, as it requires a thorough and laborious destruction of large quantities of organic tissue, and an exact analytic method. The first experiment of this kind was made on rabbit by Lombolt,[8] but no useful results were obtained, because the removal of the deposits of bismuth was not complete. Later experiments on guinea-pigs, however, gave good and consistent results.

Another method consists of determining the quantities of bismuth excreted, comparing them with the quantities located at the site of injection and thereby estimating the retention, as the difference between these quantities and the amount injected. This method, however, is less reliable, because all losses during the analysis accumulate and make the figures obtained for the retention too high.

Most of the reports of direct investigations available concerning the quantities of bismuth retained in the body deal only with the viscera, and the quantities contained in these are not large, although they have the highest concentration of the metal. The occasional investigations in the supporting tissue, muscle, bone, fat, etc., have revealed only rather small concentrations. This seems to show that the total amount of bismuth which can be stored in the organism is relatively small. This is true even when there is a beginning poisoning, and the saturation of the tissues consequently is the highest tolerated. The total amount of bismuth found in the organs as well as in the tissues by most investigators is merely a small fraction of the total quantity injected, and from a therapeutic point of view the determining factor must be "How great quantities are available in the body on the conclusion of the treatment?"

A different opinion is held by Gruhzit, Tendick and Sultzaberger [7] in their recent extensive publications. They express the opinion [9] that it is safe to assume that even a long time after the cessation of the treatment, large quantities are diffused and stored in the tissues.[10]

They arrived at this opinion through an extensive series of experiments on dogs, in which they examined the excretion in the urine and feces, and at the end of the treatment they removed the deposits at

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8. Lomholt (footnote 3, second reference).

9. Gruhzit, Tendick and Sultzaberger (footnote 7, p. 101). "The elimination was slow, and the bismuth was retained and stored in the different tissues to the extent of about 50 per cent over a period of six months."

10. A similar view was held by Mehrtens, Hanzlik and Marshalt (Proc. Soc. Exper. Biol. & Med. **25**:276, 1928) in a recent preliminary note.

the sites of injection. It was proved that the total of the two quantities determined in this way did not by any means reach the total injected quantity of bismuth. In order to obtain agreement, they assumed that the rest was stored in the tissues.

In four experiments with bismuth salicylate in oil,[11] these authors found that in the course of from twenty-four to fifty-two days only from 9 to 22.7 per cent of the injected quantity had been excreted in the urine and feces. In the corresponding sites of injection on other dogs, it was found that after from fourteen to twenty-one days only about from 7.2 to 5.2 per cent was unabsorbed. This means that more than 70 per cent of the bismuth, thus, remained unaccounted for. They assume, therefore, that this balance must be stored in other parts of the body, namely, in the muscles and in the bones.

In the organs of the abdomen, only small quantities were found, hardly more than 5 per cent of the injected quantity (it should be noted that two of the four dogs were not killed until after 189 days—and not fifty-two days).

In six dogs, small parts of the muscle tissue (about 0.5 to 1 per cent of the total quantity) were examined.[12] In one case (dog 3), the concentration of bismuth was found to be rather moderate, and in another (dog *D*), somewhat larger; but in the remaining four dogs (*2, A, B, C*) it was so considerable that the total amount of bismuth in the muscle tissue, calculated by multiplication, would be many times greater than that in all the viscera.

In another series of experiments on seven dogs, Gruhzit, Tendick and Sultzaberger examined the effect of a preparation of bismuth (bismuth thioglycolate) soluble in water. The absorption was extremely rapid in this case, only 0.3 per cent of the injected quantity being left at the site of injection after five and one-half hours. In the course of twelve hours, about 32.7 per cent of the injected quantity was recovered from the urine and feces. The excretion of only one dog was examined further for seventeen days. In this case, the excretion was somewhat slower, and the quantity recovered during this period was only 30 per cent of the amount injected. The bismuth contents of the organs and tissues of all the animals were also examined after the experiment was finished. The quantities contained in the viscera were considerably smaller than those found in the first series of experiments, and especially so in the muscles; consequently, it was impossible to account for the missing quantities of bismuth. In the bone tissue, however, a relatively large quantity of the drug was found.

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11. Gruhzit, Tendick and Sultzaberger (footnote 7, p. 90).

12. Gruhzit, Tendick and Sultzaberger (footnote 7, pp. 97 and 98, tables VIII and IX).

On this basis, these authors drew the following conclusions:[13] "It is apparent that bismuth is practically fixed in the bone which probably serves as a storage house, for the metal, as only on this basis it is possible to explain its retention in the tissue for a considerable period."

Even if this possibility is considered fully (the concrete figures have not been submitted), a considerable amount of bismuth would remain unaccounted for, and the circulation of bismuth in the body cannot be said to have been explained satisfactorily. A great number of problems in this field remain unsolved. The only way in which a final solution can be obtained is through a series of systematic experiments on animals. In each animal, an examination should be made of: (1) the total daily excretion of urine and feces, (2) the sites of injection (at the end of the experiment) and (3) all organs and tissues.

Only if one can account in a reliable way for the greater part of the injected quantity is it safe to say that a reliable result has been obtained.

For this purpose, I undertook a series of six experiments on guinea-pigs.

In all six experiments, from 80 to 97 per cent of the quantity injected was recovered. The reason for this good result was the application of a special radiochemical method[14] which makes it possible to determine the presence of bismuth, with almost absolute accuracy. A small quantity of radioactive bismuth (radium E) is added to the bismuth preparation which is to be injected. These two elements are isotopes and blend completely with each other. It is therefore necessary only to determine the radiation from the ashes of an organ, e.g., a kidney, after destruction, in order to know exactly how much bismuth it contains. The method is especially sensitive and exact, with the introduction of the following slight modification: Before the radioactivity is measured, the bismuth should be precipitated by means of hydrogen sulphide after the addition of another small constant quantity (20 mg.) of inactive bismuth; and the paper filter on which the bismuth sulphide is deposited as a homogeneous, thin black layer should be dried before the measurement.

It is important to note that this method is just as exact for small as for large quantities of bismuth, because it depends entirely on the quantities of radioactive materials added. It is possible, therefore, to obtain exactly the same accuracy whether experimenting on small animals, such as guinea-pigs or on larger ones, such as rabbits or dogs. Considerable facilitation is thus obtained in the laborious work of destruction, for instance, in the entire body of an animal.

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13. Gruhzit, Tendick and Sultzaberger (footnote 7, p. 110).

14. Christensen, Hevesy and Lomholt (footnote 3, first and second references).

Results of Experiments on Six Guinea-Pigs

	Guinea-Pig 1			Guinea-Pig 2			Guinea-Pig 3			Guinea-Pig 4			Guinea-Pig 5			Guinea-Pig 6		
Weight (at the beginning)	670 Gm.			500 Gm.			500 Gm.			500 Gm.			420 Gm.			470 Gm.		
Duration of experiment	10 days			9 days			10 days			6 days			17 days			17 days		
Total amount of bismuth injected	8 mg. in water			5 mg. in water			4 mg. in oil			5 mg. in oil			3 mg. in oil			2 mg. in oil		
Total amount of bismuth recovered	97.68 per cent			90.99 per cent			94.27 per cent			95.57 per cent			80.08 per cent			87.20 per cent		
Radioactivity per mg. (by end of experiment)	4,700			6,400			6,000			7,000			700			700		
	Weight in Gm.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.	Weight in Gm.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.	Weight in Gm.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.	Weight in Gm.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.	Weight in Gm.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.	Weight in Gm.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.
Rate of Absorption																		
Left hind-leg	15.2	1,545.74	.....	....	650.00	.....	16.3	313.33	.....	14.8	1,714.29	.....	....	71.71	.....	....	68.43	.....
Right hind-leg	15.5	2,460.43	.....	....	1,800.00	.....	17.0	760.00	.....	13.1	1,785.71	.....	....	186.71	.....	....	73.14	.....
Total bismuth in the site of injection	....	4,006.17	.....	....	2,450.00	.....	....	1,073.33	.....	....	3,500.00	.....	....	258.42	.....	....	141.57	.....
In percentage of injected bismuth	....	50.08	.....	....	49.00	.....	....	26.83	.....	....	70.00	.....	....	8.62	.....	....	7.08	.....
Distribution of Bismuth in the Body																		
Heart	2.7	0.88	0.031	1.6	6.25	0.391	1.0	1.75	0.103	1.3	2.14	0.165	2.0	1.57	0.079	1.8	0.43	0.024
Lungs	4.2	6.38	0.152	4.4	3.91	0.081	3.8	6.97	0.183	4.7	1.28	0.027	3.9	3.14	0.081	3.8	1.86	0.049
Liver	17.7	28.55	0.161	8.9	34.06	0.383	13.5	36.67	0.272	10.5	28.57	0.272	...	....	....	...	....	.....
Bile	1.0	0.06	0.006	1.9	0.31	0.16	....	.....	.....	0.85	1.50	0.176	...	....	.....	...	....	.....
Spleen	0.4	0.85	0.213	0.2	0.94	0.47	0.45	1.08	0.240	0.35	1.36	0.389	...	....	.....	...	....	.....
Left kidney	1.8	53.83	2.991	2.2	27.66	1,257	1.6	38.33	2.396	2.05	76.00	3.707	...	....	.....	...	....	.....
Right kidney	1.7	47.02	2.766	2.0	23.91	1.196	1.7	43.00	2.529	2.05	65.28	3.184	...	....	.....	...	....	.....
Testicles	....	.....	.....	3.0	0.63	0.021	...	.....	.....	1.65	2.83	0.172	...	....	.....	...	....	.....
Small intestine	....	16.55	.....	9.1	1.88	0.020	6.1	25.67	0.427	8.8	7.43	0.084	...	....	.....	...	....	.....
Great intestine	....	122.76	.....	16.6	132.19	0.796	26.3	296.64	1.128	11.5	97.86	0.851	...	....	.....	...	....	.....
Brain	4.1	0.72	0.018	3.5	2.97	0.085	4.1	0.70	0.017	3.5	3.57	0.102	...	....	.....	...	....	.....
Blood (serum)	12.5	2.55	0.020	....	.....	.....	7.0	1.78	0.025	....	.....	.....	...	....	.....	...	....	.....
Blood (cruor)	5.5	0.55	0.010	....	.....	.....	4.0	0.17	0.004	....	.....	.....	...	....	.....	...	....	.....
Bone	9.0	3.92	0.047	....	.....	.....	9.0	16.00	0.178	14.0	13.71	0.098	...	....	.....	...	....	.....
Muscle	56.0	7.00	0.013	....	.....	.....	77.5	11.97	0.016	15.0	5.57	0.037	...	....	.....	...	....	.....
Skin	65.0	22.23	0.034	45.0	13.75	0.031	50.0	14.88	0.030	55.0	(103.57)	(0.188)	...	....	.....	...	....	.....
Rest of the body	200.0	60.94	0.031	....	68.91	.....	....	28.67	.....	107.0	75.57	0.071	310	166.29	0.054	350	54.29	0.013
Total bismuth in the whole body (except site of injection.		374.74			317.17			524.31			486.24			171.00			56.57	
In percentage of injected bismuth		4.68			6.34			13.11			9.72			5.7			2.83	

Elimination in Urine

Days	Urine, Cc.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.	Urine, Cc.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.	Urine, Cc.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.	Urine, Cc.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.	Urine, Cc.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.	Urine, Cc.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.
1	76	276.76	0.359	70	142.19	0.203	25	84.17	0.337	17	53.86	0.317	60	41.29	0.069	70	153.14	0.219
2	65	271.49	0.418	75	176.25	0.235	40	144.67	0.362	85	114.00	0.134	90	144.14	0.160	65	169.71	0.264
3	42	302.77	0.721	80	181.42	0.227	65	120.17	0.185	117	144.29	0.123	98	181.29	0.186	90	90.43	0.101
4	45	245.11	0.545	40	217.50	0.544	94	342.50	0.364	55	50.57	0.092	89	196.29	0.221	100	173.71	0.174
5	280	316.38	0.396	90	158.20	0.177	67	259.17	0.387	31	58.43	0.184	70	140.57	0.201	75	61.57	0.082
6	26	282.77	1.088	65	116.09	0.179	85	175.00	0.204	15	36.56	0.244	70	101.57	0.145	60	97.29	0.162
7	35	316.17	0.903	72	122.63	0.170	128	157.50	0.123	12	40.14	0.335	20	87.86	0.439	40	73.14	0.183
8	40	346.17	0.615	50	134.06	0.268	115	171.50	0.149	..	.....	.....	120	224.29	0.186	80	151.14	0.189
9	15	221.92	1.480	6	4.84	0.081	105	249.17	0.245	..	.....	.....	55	54.43	0.099	25	28.71	0.115
10	..	.....	.....	..	.....	.....	70	146.67	0.210	..	.....	.....	62	62.43	0.101	50	37.43	0.075
11	..	.....	.....	..	.....	.....	..	.....	.....	..	.....	.....	30	50.29	0.168	25	25.71	0.103
12	..	.....	.....	..	.....	.....	..	.....	.....	..	.....	.....	..	.....	.....	30	39.86	0.133
13	..	.....	.....	..	.....	.....	..	.....	.....	..	.....	.....	77	57.43	0.075	62	39.14	0.063
14	..	.....	.....	..	.....	.....	..	.....	.....	..	.....	.....	..	.....	.....	..	.....	.....
15	..	.....	.....	..	.....	.....	..	.....	.....	..	.....	.....	55	38.86	0.071	43	43.00	0.100
16	..	.....	.....	..	.....	.....	..	.....	.....	..	.....	.....	105	46.71	0.045	14	19.43	0.139
17	..	.....	.....	..	.....	.....	..	.....	.....	..	.....	.....	10	7.57	0.076	14	12.00	0.130
Total, micrograms		2,407.54			1,253.29			1,848.52			497.85			1,435.00			1,216.45	

Elimination in Feces

	Weight in Gm.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.	Weight in Gm.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.	Weight in Gm.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.	Weight in Gm.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.	Weight in Gm.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.	Weight in Gm.	Bismuth in Micrograms	Bismuth in Mg. per 100 Gm.
1	5.5	26.17	0.476	2.0	11.72	0.586	6:5	42.17	0.649	25	51.86	0.207	....	.....	.....	....	.....	.....
2	1.5	51.92	3.461	....	.....	.....	....	.....	.....	7.7	34.86	0.453	....	.....	.....	....	.....	.....
3	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....
4	8.0	250.85	3,136	....	.....	.....	....	.....	.....	4	49.56	1.239	3	48.14	1.605	....	.....	.....
5	2.0	52.34	2.617	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....
6	19.0	186.60	0.982	....	.....	.....	....	.....	.....	2	22.00	1.100	....	.....	.....	....	.....	.....
7	13.0	192.77	1.483	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....
8	2.0	68.72	3.436	....	.....	.....	....	.....	.....	....	.....	.....	5	43.86	0.872	....	.....	.....
9	....	.....	.....	7.0	75.16	1.074	....	.....	.....	....	.....	.....	4.5	57.29	1.051	1.5	13.57	0.905
10	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....	7	66.00	0.943	2	8.82	0.441
11	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....	5	44.00	0.880	....	.....	.....
12	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....	30	117.86	0.393	37	173.71	0.470
13	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....	4.5	15.00	0.333	....	.....	.....
14	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....	36	77.86	0.216	20	48.14	0.240
15	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....
16	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....	7	7.29	0.104	....	.....	.....
17	....	.....	.....	....	.....	.....	....	.....	.....	....	.....	.....	32	44.29	0.138	7	29.86	0.427
Content of intestines	15.0	128.94	0.860	35.0	442.19	1,263	21.0	282.50	1.345	35.0	126.29	0.361	47	34.29	0.078	64	55.43	0.087
Total, micrograms		958.31			529.07			324.67			284.57			559.86			329.43	
Total elimination		3,433.85			1,782.36			2,173.19			782.42			1,994.86			1,545.88	
In percentage of injected quantity of bismuth		42.92			35.65			54.33			15.65			66.50			77.29	

The experiments were performed as follows: An intramuscular injection of from 2 to 8 mg. of bismuth in the form of bismuth oxychloride was made in each of the hind legs. The animal was put into a glass cage; the urine and feces were collected every day. The animal was allowed to bleed to death at the close of the experiment; all organs were examined, and samples were taken of all important tissues, for instance, the tissues of muscles and of bones. Both hind legs were removed for examination of the deposits of bismuth; finally, the skin, as well as the remainder of the body, was examined. The cage was washed with nitric acid, and any small quantities found in this way were distributed proportionately between the urine and feces.

Bismuth oxychloride was chosen for the experiments, as it has the advantage of being easily produced, perfectly pure and of a homogeneous, grainy appearance. In two cases, the compound was suspended in water and in four cases in oil. The quantities used as well as those recovered are noted in the table. It should be noticed that the quantities of bismuth used were up to the limit of what the animals could tolerate, as two of them (2 and 4) died spontaneously after nine and seven days, respectively. Albuminuria was not observed, so the excretion presumably followed a fairly normal course. In several cases constipation was persistent, probably as a result of the treatment but possibly it was only apparent, as some of the animals were coprophagous. Consequently, the contents of the intestines were determined by the excretion from the intestines.

COMMENT AND CONCLUSIONS

Definite conclusions regarding the problems mentioned would seem to be justified on the basis of these investigations.

The major part of the quantity injected was excreted relatively quickly with the urine and feces.

Another, not unimportant portion, somewhat varying in amount, remained at the site of injection. Only small quantities were diffused and stored in the tissues of the body, making up the "true retention." From seven to ten days later, only from 4.7 to 13.1 per cent was left, in spite of the fact that as nearly as possible, the quantities injected were the largest the animals would tolerate; thus, it is obvious that the tissues were fully saturated. After seventeen days (5 and 6), somewhat smaller quantities being used, only from 3 to 6 per cent was left. These figures were obtained from direct determinations independent of any calculation, and the fact that practically all the injected quantities have been accounted for precludes the possibility of any analytic mistake of practical importance.

From these experiments, as from practically all earlier experiments, it was learned that the major part of the bismuth in the body was

deposited in the abdominal viscera, especially in the kidneys, which showed the highest concentration; in the liver, and particularly also in the large intestine, although it should be noted that the figures for this organ are slightly excessive because it was not washed but merely scraped clean. In the rest of the body, relatively small quantities of bismuth were found, never more than 20 per cent of the total quantity in the body. It should be noted, however, that a small part of the body had been removed for examination of the sites of injection as well as for sample tests on the bones and muscles. But even if these quantities were added, the total quantity would not exceed 30 per cent of the total quantity in the body, and never more than a minimum percentage of the total injected quantity of bismuth.

The question now arises how to explain the discrepancies between these results and those obtained by Gruhzit, Tendick and Sultzaberger. Comparison shows that the difference lay almost exclusively in the results of the sample tests on the muscles, and partly, also, on the bones. According to my observations, the concentrations were extremely small, varying from 0.013 to 0.037 mg. per hundred grams for the muscle tissue and from 0.049 to 0.178 mg. per hundred grams for the bone tissue. Gruhzit, Tendick and Sultzaberger, on the other hand, showed results for the muscle tissue as high as from 0.52 to 0.91 mg. per hundred grams [15] and for the bone tissue an average of 0.19 mg.[16]

Among other observations of interest in this connection and related to earlier points of controversy, it should be mentioned that in each of the foregoing experiments on guinea-pigs the brain contained only a small quantity of bismuth. In addition, the lungs and heart showed only small, though somewhat varying, amounts; in two cases (2 and 4), the heart contained more than the lungs; in four cases (1, 3, 5 and 6), the order was reversed; this latter sequence is probably the most common, though quantities as great as those indicated by Levaditi, Girard and Manin were never found. Gruhzit, Tendick and Sultzaberger also found a varying ratio, though generally the largest quantity was revealed in the lungs.

Regarding the preference of water or oil for the suspension, these experiments do not lead to any definite conclusion, probably because the total quantities of bismuth used were so small. The results of the two experiments with water agree well: absorption of from 49 to 50 per cent occurred in from nine to ten days. When oil was used the following results were obtained: in one case, only 30 per cent was absorbed in the course of seven days; the three others showed considerably more, 73 per cent in ten days, and from 92 to 93 per cent in seventeen days;

15. Gruhzit, Tendick and Sultzaberger (footnote 7, p. 98).

16. Gruhzit, Tendick and Sultzaberger (footnote 7, p. 109, table VI).

in the latter cases, however, especially small quantities, only from 2 to 3 mg., were given. One objection against extending these conclusions to include human beings is the fact that extraordinarily weak concentrations (about 1 per cent) were used—the quantities given had to be small but still an accurate measurement had to be secured—but it is well known that weak concentrations are much more quickly absorbed than stronger ones. In therapy in human beings it is difficult to use concentrations weaker than 5 per cent, as the quantity of the injected fluid otherwise becomes too great.

SUMMARY

1. Intramuscular injections of bismuth oxychloride, two in suspensions of water and four in oil, were made in the hind legs of six guinea-pigs. The quantity of bismuth given each animal varied from 8 to 2 mg. Two animals died (no. 2 after nine days, 5 mg. of bismuth; no. 4 after seven days, 5 mg. of bismuth). The others were killed, two aften ten days and two (5 and 6) after seventeen days.

2. The bismuth content was tested by means of a special radiochemical method in: (1) the sites of injection; (2) the viscera and specimens of the muscular and bone tissue; (3) the rest of the body; (4) the daily excretion of urine and feces.

3. From 80.08 to 97.68 per cent of the total amount of bismuth injected was recovered, which permitted the formation of a reliable opinion as to the circulation of bismuth in the organism after intramuscular injection.

4. The rate of absorption varied greatly. In five cases, more than 50 per cent was absorbed after about ten days. Small injections seem to be absorbed relatively more quickly than larger ones.

5. The distribution of bismuth in the body proved to be much the same as that found by former investigators: a large concentration in the kidneys and the intestine, and a moderate concentration in the liver, spleen, etc. The skin contained only a small concentration of bismuth, and the muscular tissue still less, as shown in the table. The results of Gruhzit, Tendick and Sultzaberger on this particular point could not be confirmed. In the bone tissue, the concentration was considerably higher, though not so high as that often found by Gruhzit, Tendick and Sultzaberger. The total amount of bismuth found in the whole body (the site of injections excepted) varied from 4.68 to 13.11 per cent of the injected quantity after ten days, and from 2.83 to 5.70 per cent after seventeen days. Thus, it seems evident that the retention of bismuth in the body cannot be considered a predominant factor in therapy.

6. The rate of elimination corresponded well with that of absorption.

SCLERODERMA

WITH SPECIAL REFERENCE TO ITS ETIOLOGY AND TREATMENT *

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The early history of scleroderma is confused with that of leprosy, ichthyosis and keloid. Under the name of ichthyosis corii, Curzio,[1] in 1752, described a case which was probably diffuse scleroderma. Alibert [2] and Addison,[3] under the name of true keloid, distinguished the localized form of scleroderma from false keloid, the latter being what is now called keloid. Henke [4] described the infantile form of the disease clearly and in a footnote gave a typical case of the diffuse type in the adult. He called it Verhaertung des Zellgewebes or induratio telae cellularis. Fagge [5] reported an interesting postmortem examination of the skin and liver in a case of diffuse "scleriasis." T. C. Fox [6] gave an interesting account of the early history of the disease. In 1895, Lewin and Heller [7] reviewed the whole subject up to that date, collecting reports of more than 500 cases from the literature, including 12 new ones of their own. Notthafft,[8] in 1898, and Luithlen,[9] in 1904, again summed up the subject completely, the latter giving an exhaustive account of the various subjective and objective clinical signs of the disease.

Authorities still separate the localized form, morphea, from the generalized or diffuse symmetrical type; however, there is no distinction

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1. Curzio: Dissertation anatomique et pratique sur une maladie de la peau d'une espèce fort rare et fort singulière, 1752, quoted by Notthafft, Centralbl f. allg. Path. u. path. Anat. **9**:370, 1898.

2. Alibert, J. L.: Clinique de l'hôpital Saint Louis ou traité complet des maladies de la peau, Paris, 1833, p. 210.

3. Addison, T.: On the Keloid of Alibert and on True Keloid, M. Chir. Tr. **37**:27, 1854.

4. Henke, A.: Handbuch zur Erkenntniss und Heilung der Kinderkrankheiten, Frankfort-on-the Main, 1809, p. 141.

5. Fagge, C. H.: Specimen of Skin and Liver from a Case of Diffused Scleriasis, Tr. Path. Soc., London **22**:309, 1871.

6. Fox, T. C.: Note on the History of Sclerodermia in England, Brit. J. Dermat. **4**:101, 1892.

7. Lewin, G., and Heller, J.: Die Sklerodermie; eine monographische Studie, Berlin, A. Hirschwald, 1895.

8. Notthafft, A. F.: Neuere Arbeiten und Aussichten ueber Sklerodermie, Centralbl. f. allg. Path. u. path. Anat. **9**:870, 1898.

9. Luithlen, F.: Sklerodermie, in Franz Mraçek: Handbuch der Hautkrankheiten, 1904, vol. 3, p. 128.

pathologically (Crocker [10]), and cases of local and diffuse forms in the same patient are reported (Duckworth [11] and Stowers [12]). Clinically, the two are quite distinct, the diffuse forms being much more severe and comparatively rare. Some of them, especially those starting at the fingers or toes, are chronic and last for twenty or thirty years before a definite diagnosis is possible; others start with acute pain and swelling of the affected parts, the process extending rapidly day by day until large areas are involved in a comparatively short time. Elevation of the temperature is unusual, but a septic type of fever is occasionally observed. This may, however, be due to some underlying or concomitant condition. Whether acute or chronic, there is usually marked symmetry of the lesions. Involvement of the mucous membranes is rarely observed (Hoppe-Seyler,[13] Hektoen,[14] Lutati [15] and Maier [16]). Lesions of the mouth seen in some cases are apparently due, not to scleroderma, but to the difficulty in keeping the mouth clean or to the general malnutrition. The latter suggests conditions seen in so-called secondary or pseudo pellagra. Whether in the form starting with infiltration or in the edematous type, the diagnosis is made clinically by the firm inelastic feeling of the part with its shiny, wax-model look, and either a yellowish white or, especially in the edematous stage, a pink color. The atrophic stage, chiefly and possibly only seen after the edematous type, is encountered particularly on the fingers and toes (sclerodactylia) and is practically indistinguishable from a late case of Raynaud's disease. Indeed, some authorities consider that they are manifestations of the same pathologic process.

SCLERODERMA AND TRAUMA

In regard to the etiologic factors in scleroderma, trauma of various sorts has preceded the onset in many cases, as noted in cases starting on the hands of stonecutters (Bramwell [27]) or after accidents (Der-

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10. Crocker, H. R.: The Histology and Pathology of Morphea and Its Relation to Scleroderma Adultorum, Tr. Path. Soc., London **31**: 315, 1880.

11. Duckworth, D.: Case of Scleroderma Adultorum Illustrating Circumscribed and Diffuse Forms of Malady, Tr. Path. Soc., London **31**:322, 1880.

12. Stowers, J. H.: Mixed Scleroderma, Brit. J. Dermat. **17**:106, 1905.

13. Hoppe-Seyler, G.: Deutsches Arch. f. klin. Med. **44**:581, 1889.

14. Hektoen, L., and Wells, H. G.: Ein Fall von Skleroderma diffusum in Verbindung mit chronischen, fibroesen, Veraenderungen in der Schilddruese, Centralbl. f. allg. Path. u. path. Anat. **8**:673, 1897.

15. Lutati, K. V.: Beitrag zum Studium der Sklerodermie der Zunge und der Mundschleimhaut, Dermat. Ztschr. **20**:682, 1913.

16. Maier: Ein Fall von Sklerodermie, Klin. Wchnschr. **5**:386, 1926.

17. Bramwell, B.: Diffuse Scleroderma: Its Frequency; Its Occurrence in Stone Masons; Its Treatment with Fibrolysin, Edinburgh M. J. **12**:387, 1914.

cum,[18] Schwerdt,[19] Sequeira [20] and Pernet [21]). Walker [22] recorded a case of the localized type following the painting of the part with iodine, but he admitted that it was not entirely clear that the pain and stiffness for which the iodine was applied were not the premonitory signs of the scleroderma. The same might be said of the case of Eddowes,[23] in which irritating plasters and liniments were applied for a toothache, and scleroderma developed on that side of the neck and face. Severe sunburn (Fox [24]) and x-ray dermatitis (Schwarz [25] and Maier) are among the antecedents mentioned as causative of scleroderma. Exposure to cold was considered to be of fairly frequent etiologic importance or a determining factor by Gordinier,[26] Ravogli [27] and Dercum, but the latter called attention to the fact that the exposure to cold may be purely coincidental and without etiologic significance. Hoppe-Seyler considered frostbite of the feet as the underlying cause which weakened the tissues at the onset in one of his cases.

SCLERODERMA AND THE NERVOUS SYSTEM

The nervous system is an important factor in a fairly large number of cases of scleroderma. Savill [28] and Schwarz found underlying hereditary nervous tendencies which they considered noteworthy. Dercum quoted a case in which scleroderma followed a sudden fright on account of a fire and thought that the consequent psychic shock was the determining factor. Every part of the nervous system has been involved in one or another of the reported cases. Streatfield,[29] Anderson,[30]

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18. Dercum, F. X.: Scleroderma, J. Nerv. & Ment. Dis. **23**:431, 1896.

19. Schwerdt: Weitere Faelle von Sklerodermie, behandelt mit Mesenterialdruesen, München. med. Wchnschr. **54**:1230 (June 18) 1907.

20. Sequeira: Brit. J. Dermat. **19**:242, 1907; **20**:198, 1908.

21. Pernet, G.: Case of Unilateral Band Scleroderma and Morphea: Scleroderma of Left Leg, Proc. Roy. Soc. Med. **12**:43, 1919.

22. Walker: Scleroderma, J. Cutan. Dis. **34**:231, 1916.

23. Eddowes, A.: Atrophic Cutaneous Affections, M. Press & Circular **111**:49, 1921.

24. Fox, W.: Case of Morphea Guttata, Proc. Roy. Soc. Med. **15**:14, 1922.

25. Schwarz, P.: Sklerodermie und Roentgenkastration, Schweiz. med. Wchnschr. **7**:246, 1926.

26. Gordinier, H. C.: A Case of Sclerodactyle with Diffuse Scleroderma, Am. J. M. Sc. **97**:15, 1889.

27. Ravogli, A.: On a Rare Form of Scleroderma, J. Cutan. Dis. **35**:1 (Jan.) 1917.

28. Savill, T. D.: Scleroderma of the Extremities Associated with Angioneurotic Edema, Proc. Roy. Soc. Med. **2**:200, 1909.

29. Streatfield: M. Times & Gaz. **1**:703, 1880.

30. Anderson, W.: Brit. J. Dermat. **10**:46, 1898.

Lion,[31] Bunch [32] and Castle [33] have reported lesions following the course of the fifth nerve. Sequeira [34] and O'Donovan [35] reported cases involving more than one branch of the fifth nerve, and reasoned that there must be a lesion of the gasserian ganglion. The following case illustrates localized scleroderma with frontal nerve distribution:

CASE 1.—*History.*—H. B., an American schoolgirl, aged 9, presented an unimportant family history and an unimportant past history, except that she was said to have always had a subnormal temperature.

Five years before examination, a spot appeared on the left side of the scalp; it slowly increased in size. Two months before examination, a new spot appeared on the left eyebrow.

Examination.—An area, 6 by 1 cm., was present on the middle third of the left eyebrow; it was raised, firm, ivory white and extended up on the forehead. The area was bald with bluish depressions resembling enlarged sebaceous glands. In the hairy region of the scalp, about in line with this lesion, was a grooved area extending backward; it was 1.5 by 8.5 cm. in diameter and was bald in the center with scattered stiff, irregular hairs on the posterior end and a few scattered hairs on the sides. The area was atrophic, depressed and ivory white and was bound down to the underlying tissues. The rest of the hair was dry, and the scalp was slightly scaly.

The patient was given 1 grain (0.065 Gm.) of thyroid substance three times daily.

In six weeks, the hair was returning on the eyebrow, and the scar was more pliable. In five months, the spot on the eyebrow was nearly gone. The skin of the lesion on the scalp was softened and healthier, but there was no hair on it.

Leri and Lamy [36] found involvement of the spinal nerve roots. Bruns [37] described a case in which the distribution corresponded to spinal nerve segments. Steven [38] reported cord lesions of the anterior horns at autopsy in one case. Mayer [39] reported a case showing sensory changes which resembled syringomyelia and suggested a possible lesion

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31. Lion: Monatsh. f. prakt. Dermat. **34**:580, 1902.

32. Bunch, J. L.: Brit. J. Dermat. **21**:24, 1909.

33. Castle, W. F.: The Endocrine Causation of Scleroderma Including Morphea, Brit. J. Dermat. **35**:255 and 303, 1923.

34. Sequeira, J. H.: Two Cases of Fronto-Nasal Morphea with Remarks, Brit. J. Dermat. **23**:40, 1911.

35. O'Donovan, W. J.: Facial Morphea, Brit. J. Dermat. **27**:377, 1915.

36. Leri, A., and Lamy, L.: Vitiligo zoniform du flanc droit; sclérodermie en bande avec atrophie en masse du membre inférieur gauche, Bull. soc. franç. de dermat. et syph. **30**:127 (March 8) 1923.

37. Bruns, L.: Ueber einen Fall von diffuser Sklerodermie der Beine mit schärfer spinal-segmentaerer Abgrenzung nach oben, Deutsche med. Wchnschr. **25**:487, 1899.

38. Steven, J. L.: Case of Scleroderma Adultorum, Glasgow M. J. **26**:280, 1886. Case of Scleroderma with Pronounced Hemiatrophy of the Face, Body and Extremities, ibid. **50**:401, 1898.

39. Mayer: Wien. klin Wchnschr. **22**:552, 1908.

of the cord as the cause of the scleroderma. Jacquet [40] described a diffuse case showing marked lesions of the spinal cord (myélite cavitaire) at autopsy. Sternberg [41] suggested that the changes in the blood vessels in persons with scleroderma were like those found in persons with disease of the central nervous system, but admitted that the connection of these peripheral blood vessel changes with diseases of the cord was not yet known. Josephowitch [42] described a unilateral case in a patient suffering with jacksonian epilepsy and said that the condition of the skin must be cerebral in origin. Jeanselme and Touraine,[43] and Castle thought that there is a lesion of the nervous system in some cases. The more recent writers, Lortat-Jacob, Legrain and Baudoin,[44] Guillain,[45] Heimann,[46] and Curschmann,[47] expressed the belief that there is probably some injury or disturbance of function of the sympathetic nervous system. Osler [48] thought that a trophoneurosis, dependent on changes in the nervous system, was the most workable theory. At the conclusion of his study, Luithlen also thought that a trophoneurosis was probably the most important etiologic factor.

SCLERODERMA AND VASCULAR SYSTEM

Hutchinson [49] was the first to note changes in the blood vessels, especially in the capillaries, and since then, Durham [50] has shown marked involvement of the blood vessels post mortem. Bertin [51] found changes in the blood vessels and mentioned the fact that the latter frequently have been found by other authors. Brown [52] noted changes in the

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40. Jacquet: Bull. soc. franç. de dermat. et syph. **24**:359 (July 3) 1913.

41. Sternberg: Wien klin. Wchnschr. **22**:552, 1908.

42. Josephowitch: Hemiscleroderma, Russk. J. Kozhn. i. Ven. Boliezn. **28**:232, 1914; abstr., J. Cutan. Dis. **34**:480, 1916.

43. Jeanselme, E., and Touraine, A.: Syphilis et sclérodermie, Bull. soc. franç. de dermat. et syph. **24**:351 (July 3) 1913.

44. Lortat-Jacob; Legrain, P., and Baudoin, E.: Sclérodermie généralisée d'origine syphilitique, Bull. soc. franç. de dermat. et syph. **30**:398 (Nov. 8) 1923.

45. Guillain, G.; Alajouanine, T., and Marquezy, R.: Sclérodermie progressive avec cataracte double précoce chez un infantile, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:1489 (Nov. 9) 1923.

46. Heimann, H. W.: Zur Aetiologie der Sklerodermie: universelle Sklerodermie bei hypophysaeren Zwergwuchs, Med. Klin. **21**:1082 (July 17) 1925.

47. Curschmann, H.: Zur Behandlung der Sklerodermie, Therap. d. Gegenw. **67**:249, 1926.

48. Osler, W.: On Diffuse Scleroderma; with Special Reference to Diagnosis and to the Use of Thyroid Gland Extract, J. Cutan. Dis. **16**:49 and 127, 1898.

49. Hutchinson, J.: M. Times & Gaz. **1**: 347, 1884.

50. Durham, R. H.: A Case of Scleroderma with Extensive, Subcutaneous, Periarticular and Vascular Calcification, Ann. Clin. Med. **5**:679, 1927.

51. Bertin, E.: Les rapports de la syphilis et de la sclérodermie, Ann. de dermat. et syph. **7**:175 (March) 1926.

52. Brown, G. E., and O'Leary, P. A.: Skin Capillaries in Scleroderma, Arch. Int. Med. **36**:73 (July) 1925.

capillaries intra vitam in persons with scleroderma and Raynaud's disease. Audry [53] thought that an angiotrophoneurosis is present both in scleroderma and in Raynaud's disease. In this connection, numerous authors have found scleroderma and Raynaud's disease combined (Brouhin,[54] White,[55] Osler, Claude,[56] Moutrier,[57] Giroux,[58] Berk [59] and McKay.[60] In a postmortem examination on two patients with scleroderma, Alquier and Touchard [61] found early inflammatory changes about the blood vessels of the internal organs leading to ischemia and later to sclerosis of the skin. According to these authors, when the endocrine glands are thus affected, many of the well recognized symptoms of the disease follow as a result of their malnutrition.

In 1872, Heller [62] reported a case in which there was obstruction of the thoracic duct and its branches with fibrous growths, and reasoned from this that the scleroderma in his case was due to this obstruction and so allied to elephantiasis. Like the latter, he thought that scleroderma followed blocking of the lymphatics by repeated inflammatory conditions such as erysipelas. I have been unable to find further cases to confirm this hypothesis.

SCLERODERMA AND THE ENDOCRINE SYSTEM

Closely allied to the cases showing changes in the sympathetic system and those showing angioneurosis are those in which disturbance of the endocrine glands has occurred. Huisemann [63] stated that scleroderma undoubtedly belonged to the category of disturbances of the endocrine glands, the latter being due to some infection of the sympathetic nervous system which acted as a nutritive center for the glands and blood ves-

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53. Audry, C., and Chatellier, L.: Sclérème des adultes et syphilis, Ann. de dermat. et syph. **4**:1 (Jan.) 1923.

54. Brouhin: Gaz. d. hôp. **51**:250 (March 16) 1878.

55. White, J. H.: Notes on a Case of Combined Scleroderma and Raynaud's Disease, Lancet **1**:1136, 1896.

56. Claude, R., and Touchard, P.: Maladie de Raynaud, sclérodermie et rhumatisme chronique, Bull. et mém. Soc. méd. d. hôp. de Paris **24**:277 (March 15) 1907.

57. Moutrier, J. P.: Syndrome de Maurice Raynaud et Sclérodermie, Thèse, Paris, 1910.

58. Giroux, L.: Maladie de Raynaud et syphilis, Ann. d. mal. vén. **8**:881 (Dec.) 1913.

59. Berk: J. Cutan. Dis. **32**:379, 1914.

60. McKay, H.: Scleroderma and Its Treatment by Radium, Canad. M. A. J. **16**:142, 1926.

61. Alquier, L., and Touchard, P.: Lésions des glandes vasculaires sanguines, Arch. d. méd. expér. **19**:687, 1907.

62. Heller, A.: Ein Fall von Sklerodermie als Beitrag zur Pathologie des Lymphgefaesssystems, Deutsches Arch. f. klin. Med. **10**:141, 1872.

63. Huisemann, L.: Ueber die Beziehungen von Infektion, Gefaess- und Blutdruesenerkrankungen zur Sklerodermie, München. med. Wchnschr. **52**:451, 1905.

sels. Schwerdt reports the case of an infant which at autopsy showed enlarged and red mesenteric glands. He also reports five cases in which improvement followed the administration of mesenteric gland extract by mouth, but two of these were in children among whom spontaneous recovery is the rule. Kolle [64] also reported a case in which marked improvement followed the use of a similar gland extract.

Audry quoted a case in which he thought there was a disturbance of the hepatic endocrine function.

Jeanselme [65] described a case of ovarian insufficiency in which the patient was nearly cured of the scleroderma by ovarian gland therapy. Mosenthin [66] quoted a case in a woman who had a malignant disease of both ovaries which were removed surgically; the operation was followed by scleroderma of the face, arms and legs. Ehrmann [67] mentioned two cases in which marked ovarian disease was present, but both showed fibrous or cystic changes in the thyroid also.

Struempell [68] brought out several facts to show that scleroderma is in some ways the antithesis of acromegaly, and suggested the possibility of the relation of the former to the endocrine glands, particularly the pituitary. He described a case of generalized scleroderma in a hypophyseal dwarf. Schwartz [69] quoted six cases of localized and generalized scleroderma, all showing increased sugar tolerance and improvement after administration of pituitary extract. Trimble [70] and Heimann [71] also claimed some success with treatment by pituitary extract.

On account of the pigmentation frequently seen in scleroderma, particularly in the diffuse type of the disease, pathologic changes in the suprarenal gland are often considered. Towle [72] and Rothmann [73]

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64. Kolle, W.: Weiteres zur Behandlung der Sklerodermie mit Coeliacin, München. med. Wchnschr. **60**:24 (Jan. 7) 1913.

65. Jeanselme, E., and Burnier, R.: Sclérodermie en Plaques avec dyschromie pigmentaire symmetrique, Bull. soc. franç. de dermat. et syph. **33**:704 (Dec. 9) 1926.

66. Mosenthin, H.: Ein Fall von Sklerodermia, seine Beziehungen zur innere Sekretion und Bemerkungen ueber die Aetiologie dieser Erkrankung, Arch. f. Dermat. u. Syph. **118**:613, 1913.

67. Ehrmann, S.: Demonstration von Praeparaten von diffuser Sklerodermie, Arch. f. Dermat. u. Syph. **151**:428, 1926.

68. Struempell, A.: Ein Beitrag zur Pathologie und pathologischen Anatomie der Akromegalie, Deutsche Ztschr. f. Nervenh. **11**:51, 1897.

69. Schwartz: Cases of Morphea and Scleroderma, J. Cutan. Dis. **35**:256, 1917.

70. Trimble: J. Cutan. Dis. **35**:257, 1917.

71. Heimann, H. W.: J. Cutan. Dis. **35**:256, 1917.

72. Towle, H. P.: Clinical Report from the Wards for Skin Diseases at the Massachusetts General Hospital, Boston M. & S. J. **151**:629, 1904.

73. Rothmann: Ueber endokrine Stoerungen bei Sklerodermie, Berlin, Klin. Wchnschr. **4**:1691 (Aug. 27) 1925.

quoted cases of this order. Winfield [74] described a case in which postmortem examination showed tuberculosis of the suprarenals. Osler quoted a case of Addison's disease in connection with scleroderma and also mentioned one with sudden death described by Schultz as supporting the theory of suprarenal disease. Winfield,[75] Roesch [76] and Tedeschi [77] all quoted cases in which improvement followed treatment with suprarenal gland, although in Roesch's case there was evident abnormal thyroid function in addition to signs of suprarenal trouble. In this connection, the following case is reported:

CASE 2.—*History.*—K. K., aged 31, born in Greece, a housewife, was first seen in the skin outpatient department of the Boston City Hospital, Nov. 22, 1927. The family history was unimportant. She did not have any of the usual diseases of childhood. She was married in 1911. An operation (probably left salpingo-oophorectomy) was performed the same year.

For four or five years, the hands and feet had been cold, numb and blue, especially when wet or cold. Gradual thickening of the skin and underlying tissues occurred. For two years she had noticed gradually increasing pigmentation of the skin and frequent coryza and lacrimation. Perspiration was usually scanty. The menses were regular. She had taken a great deal of medicine the nature of which was unknown, except that in the winter of 1926, just before the time of onset of pigmentation, she received twelve injections, probably of sodium cacodylate.

Physicial Examination.—The patient was well developed and nourished. The teeth were good; the sinuses were normal; the mucous membrane of the mouth was normal; the tonsils were slightly congested. Moderate coryza with congestion of the eyelids and lacrimation was present; the eyes, including examination of the fundi, were otherwise normal. The abdomen was normal, except for slight tenderness over the laparotomy scar in the left lower quadrant; the reflexes and joints were normal. The skin was dry and was pigmented to a degree of moderate tan, the color fairly evenly distributed but more marked on the exposed parts. The hands would become blue and fade out again while under observation. The skin of the hands, arms, feet, legs, face and chest was thickened, firm and swollen, but did not pit on pressure. It was not tender.

The Wassermann and Kahn tests were negative. Examination of the blood showed: white cell count, 6,000; red cell count, 5,952,000; hemoglobin, 95 per cent. The smear showed: polymorphonuclears, 66 per cent; lymphocytes, 30 per cent; large mononuclears, 4 per cent. Otherwise the blood was normal.

The metabolic rate was plus 11 per cent, and two months later, it was plus 5 per cent.

A sugar tolerance test showed: fasting blood sugar, 0.136; one hour after dextrose meal, 0.207; two hours after dextrose meal, 0.149. The blood calcium

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74. Winfield, J.: J. Cutan. Dis. **35**:256, 1917.

75. Winfield, J.: A Case of Scleroderma with Symptoms Simulating Addison's and Rayanud's Diseases, J. Cutan. Dis. **22**:586, 1904. A Case of Scleroderma Improved under the Use of Dessicated Suprarenal Gland, ibid. **22**:587, 1904.

76. Roesch, W.: Ueber die Beziehungen der Sklerodermie zu den Erkrankungen der endokrinen druesen, Deutsche med. Wchnschr. **45**:1329 (Nov. 27) 1919; abstr., J. A. M. A. **74**:989 (April 3) 1920.

77. Tedeschi, E.: Richerche sul Ricambio Materiale in un Caso di Sclerodermia, Riforma med. **3**:75, 1901.

was 9.5 mg. per hundred cubic centimeters. The pulse rate was from 86 to 98. The blood pressure ranged from 116 systolic, 80 diastolic to 105 systolic, 75 diastolic. The condition was diagnosed as scleroderma.

The neurologist made the diagnosis of disturbance of the sympathetic nervous system (thoracic lumbar region) and possible suprarenal dysfunction. There was some question of arsenic poisoning.

Treatment and Course.—The patient was given ephedrine solution by mouth. In one month, there was decided improvement which continued until the lesions nearly cleared up. Calcium lactate was also given for two weeks but was stopped on account of nausea.

Since Singer,[78] in 1895, reported a case, there have been a large number of cases of scleroderma mentioned in connection with thyroid disease—thyroid atrophy (Hektoen,[79] Uhlenhuth,[80] Claude, Dupré,[81] Brocq,[82] Rothman, Guillain, and Ehrmann), thyroid enlargement (Vincent,[83] Roesch) and exophthalmic goiter (Osler, Hyde,[84] Ziegel,[85] Foerster[86] and Sequeira[87]). Some cases have shown a slight or marked improvement under thyroid treatment, like case 1 of my own (Graham-Little,[88] Goodman,[89] Nicolas[90] and Lousté[91]); other patients

78. Singer, G.: Zur Pathologie der Sklerodermie, Berl. klin. Wchnschr. **32**:226 (March 18) 1895.

79. Hektoen, L.: Diffuse Scleroderma Associated with Fibrous Changes in the Thyroid and Great Diminution in the Amount of Thyroidin, J. A. M. A. **28**:1240 (June 26) 1897.

80. Uhlenhuth: Ueber diffuse Sklerodermie, Berl. klin. Wchnschr. **36**:207, 1899.

81. Dupré and Kahn, P.: Sclérodermie et maladie de Raynaud (syndrome polyglandulaire), Bull. et mém. Soc. méd. d. hôp. d. Paris **27**:1230, 1909.

82. Brocq, L.; Fernet and Maurel: Sclérodermie diffuse à développement rapide dans le cours de la syphilis secondaire, Bull. soc. franç. de dermat. et syph. **24**:347 (July) 1913.

83. Vincent, H.: Atrophie thyroidienne et sclérodermie consécutive au rheumatisme, Bull. et mém. Soc. méd. d. hôp. de Paris **24**:282 (March 15) 1907.

84. Hyde, J. N., and McEwen, E. L.: The Dermatoses Occurring in Exophthalmic Goiter, Am. J. M. Sc. **125**:1000, 1903.

85. Ziegel, H. F.: A Case of Graves' Disease with Scleroderma and a Positive Wassermann Reaction, Treated with Salvarsan, M. Rec. **83**:1124 (June 21) 1913.

86. Foerster, O. H.: Relation of Internal Secretions to Cutaneous Disease, J. Cutan. Dis. **34**:1 (Jan.) 1916.

87. Sequeira, J. H.: Four Cases of Scleroderma Associated with Disease of the Thyroid Gland, Brit. J. Dermat. **28**:31, 1916.

88. Graham-Little, E. G.: Case of Scleroderma Associated with Graves' Disease and Later Myxedema, Proc. Roy. Soc. Med. **9**:69, 1915-1916; also in Brit. J. Dermat. **28**:124, 1916.

89. Goodman, H.: Scleroderma Diffusa in a Girl Nine Years of Age, J. Cutan. Dis. **36**:210, 1918.

90. Nicolas, J., and Moutot, H.: Sclérodermie en plaques à forme mixte, lardacée et tubéreuse, avec guérison par la thyroidine, Ann. de dermat. et syph. **3**:344, 1912.

91. Lousté: Bull. soc. franç. de dermat. et syph. **30**:402 (Nov. 8) 1923.

have either not improved or have been made worse (Atwater [92]). Pusey [93] expressed the belief that thyroid is not often useful. Osler found that it is not of much use but might well be tried. Two of his six patients were improved by it. Sequeira reported a case of myxedema in which the patient improved under thyroid treatment which she took for fifteen years. She then developed scleroderma while thyroid therapy was still being used and while the myxedema was under control. Roques [94] analyzed sixty-seven cases of diffuse and ten of localized scleroderma in which the patients were treated with thyroid and found cures in 6 per cent of the diffuse cases, improvement in 48 per cent and failure of the treatment in 46 per cent; in the localized cases, one patient was cured, six were improved, and in three the treatment failed. In many cases, the condition was apparently arrested but not benefited beyond that.

If one considers all these cases which show involvement of the endocrine glands together, it seems likely that there is a pluriglandular trouble in many of them (Foerster, Castle, and Schwarz). It is a common occurrence to note the vicarious action of these endocrine glands and the effects on other glands of treatment with the single gland extracts.

Ayres [95] and Berkowitz [96] mentioned cases of both the diffuse and the localized type in which arsenic was found in the urine, usually after long exposure to arsenical dyes or following prolonged use of arsenic internally. A much longer series of cases is needed to prove anything in this direction when arsenic is so frequently found in the urine of patients taken at random. However, Ayres showed an interesting parallelism of the symptoms of arsenic poisoning and scleroderma. Case 2 of my own suggests the possibility of arsenic poisoning following the use of sodium cacodylate.

SCLERODERMA AND TOXIC CONDITIONS

Chronic arthritis is frequently reported (Duckworth, Hoppe-Seyler, White, Vincent, and Dupré), either preceding the scleroderma or accompanying it, which suggests the possible toxic origin of the disease. Cases arising during pregnancy and during lactation might also be considered

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92. Atwater, R. M.: Scleroderma and Sclerodactyly: Report of a Case with Roentgen Rays and Review of the Literature, Am. J. M. Sc. **158**:29 (July) 1919.

93. Pusey, W. A.: J. Cutan. Dis. **39**:9 (Jan.) 1917.

94. Roques, E.: Le traitement opothérapeutique de la sclérodermie, Ann. de dermat. et syph. **1**:383, 1910.

95. Ayres, S.: Scleroderma as a Possible Manifestation of Chronic Arsenic Poisoning, Arch. Dermat. & Syph. **2**:747 (Dec.) 1920.

96. Berkowitz: Scleroderma and Sclerodactylia, Arch. Dermat. & Syph. **14**:204 (Aug.) 1926.

as manifestations of toxemia (Fox [97] and Castle). Castle found severe caries of the teeth in several of his cases and suggested that this may have an etiologic bearing, and Graham-Little [98] published a report of a case which showed marked improvement after the removal of septic teeth. Graham-Little [99] and Meakins [100] mentioned cases showing gastro-intestinal disorders which might be sources of toxemia. The latter's patient improved markedly under a properly balanced diet. Curschmann [101] quoted a case showing cholecystitis and a possible early cancer of the bladder. Adamson,[102] Savill, Davis [103] and Schwarz all considered the importance of toxemia as an etiologic factor, and Pernet and Crocker, in discussing Adamson's case, confirmed the possible toxic origin.

SCLERODERMA AND INFECTIOUS DISEASES

Cockayne [104] stated that the process, especially in the diffuse cases, sometimes involves the underlying muscles primarily (dermatomyositis), and he maintained that this type is probably due to a local infection. Reports of many cases are published in which there is an underlying or preceding infectious disease: typhoid (MacKenzie [105]); bronchopneumonia (Sequeira); chorea (Lousté [106]); acute articular rheumatism (Pernet, MacCallum [107]); pneumonia (Langmead [108]), and pulmonary tuberculosis (Finlay,[109] Hektoen, Notthafft, Claude, Alquier, Engelmann [110] and Castle). Castle also mentioned reports of cases

97. Fox, H.: Localized Scleroderma: Unilateral Pigmentation, J. Cutan. Dis. **34**:308, 1916.

98. Graham-Little, E. G.: Case of Very Extensive Scleroderma, Proc. Roy. Soc. Med. **16**:64, 1923.

99. Graham-Little: Scleroderma of the Diffuse Type, Brit. J. Dermat. **22**:57, 1910.

100. Meakins, J.: Tr. A. Am. Phys. **41**:202, 1926.

101. Curschmann, H.: Sklerodermie mit Oedem, München. med. Wchnschr. **72**:2216 (Dec.) 1925.

102. Adamson, H. G.: Case of Sclerodermia (Morphea), Brit. J. Dermat. **20**:230, 1908.

103. Davis, H.: Case of Scleroderma, Proc. Roy. Soc. Med. **16**:29, 1922.

104. Cockayne, E. H.: Congenital and Acquired Scleroderma in Childhood, Brit. J. Child. Dis. **13**:225 (Aug.) 1916.

105. MacKenzie: Brit. J. Dermat. **19**:405, 1907.

106. Lousté, Cailliau and Leclerc: Un cas de sclérodermie subaiguë survenu dans la convalescence d'une chorée, Bull. soc. franç. de dermat. et syph. **32**:273 (June 14) 1925.

107. MacCallum, W. G.: Acute Diffuse Scleroderma, Tr. A. Am. Phys. **41**:190, 1926.

108. Langmead, F. S.: Scleroderma with Calcification in a Mongol, Proc. Roy. Soc. Med. **12**:94, 1919.

109. Finlay, D. W.: Scleroderma, Brit. J. Dermat. **1**:339, 1889.

110. Engelmann: Wien. klin. Wchnschr. **22**:552, 1908.

which he has found in the literature following sepsis, scarlatina, measles, malaria and tonsillitis. Since the study of syphilis has been awakened by the Wassermann reaction, it is interesting to note how frequently syphilis has been found in persons with scleroderma. Sometimes it is found after early syphilis (Brocq, Murray-Will [111]), sometimes after late syphilis (Williams,[112] Ziegel, Gaskell,[113] Lortat and Leri [114]), and even in hereditary syphilis (Jackson,[115] Jeanselme, Milian,[116] Roudinesco,[117] and Foster [118]). As far back as 1884, Hutchinson mentioned what was probably a case of sclerodactylia in a syphilitic patient. It is interesting to observe how many of these cases of syphilis in connection with scleroderma show positive signs of syphilis in the spinal fluid. Liebner,[119] Audry and Lortat reported cases of cerebrospinal syphilis in which scleroderma was present. Bertin collected from the literature a long list of cases of scleroderma in connection with syphilis and felt that this clinical fact proves beyond discussion the syphilitic etiology of some cases of scleroderma. Skinner [120] discussed the close relationship of syphilis and scleroderma in many cases and also of Raynaud's disease with both of these. Whitehouse [121] found positive Wassermann reactions in three of his five patients with diffuse scleroderma and weak reactions in the other two, the latter having been under previous antisyphilitic treatment. He also called attention to the pathologic similarity of the two, especially in regard to infiltration about the blood vessels. Schamberg,[122] in discussing a case reported by Gaskell, said that so many of these cases show positive Wassermann reactions that he thinks that they are all syphilitic in origin. In the same discussion, Dr. Hartzell stated that in his opinion so many of the cases show

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111. Murray-Will E.: Sclerodermia and Syphilis, Brit. J. Dermat. **39**:201 (May) 1927.

112. Williams, A. W.: Brit. J. Dermat. **22**:361, 1910.

113. Gaskell: Scleroderma, J. Cutan. Dis. **34**:465, 1916.

114. Leri, A., and Barthélémy, R.: Sclérodermie progressive chez une Syphilitique. Bons effets du traitement bismuthique, Bull. soc. franç. de dermat. et syph. **31**:186 (April 10) 1924.

115. Jackson: Two Cases of Scleroderma, J. Cutan. Dis. **27**:161, 1909.

116. Milian: Bull. soc. franç. de dermat. et syph. **24**:359 (July 3) 1913.

117. Roudinesco and Vallery-Radot, P.: Sclérodermie mutilante progressive, Bull. soc. franç. de dermat. et syph. **30**:151 (March 8) 1923.

118. Foster, E., and Giustinian, V.: Un Caso de Escleroedema Congénito Generalizado (Ictericia; Heredosifilis; Polidactilia), Semana méd. **32**:821 (Oct. 1) 1925.

119. Liebner, E.: Ein Fall von Sklerodermie mit Syphilis, Dermat. Wchnschr. **83**:1195 (Aug. 14) 1926.

120. Skinner, E. F.: Brit. J. Dermat. **37**:459 (Nov.) 1925; **37**:507 (Dec.) 1925.

121. Whitehouse, H. H.: J. Cutan. Dis. **27**:535 (Dec.) 1909; abstr., J. A. M. A. **54**:412 (Jan. 29) 1910.

122. Schamberg: J. Cutan. Dis. **34**:465, 1916.

changes in the ductless glands, particularly the thyroid, that this must be an important factor. Supporting syphilis as an etiologic factor is the effect of antisyphilitic treatment in some cases. Hillairet [123] quoted a case accompanied by a sclerodactylia in which a complete cure was effected except for a permanent rigidity of some of the fingers. Leri reported a late case in which great improvement occurred after treatment with bismuth compounds. Improvement, more or less marked, was noted by Hutchinson, Lang,[124] Millard,[125] Williams, Ziegel, Jeanselme, Milian,[126] Lortat, Audry, Skinner,[120] Liebner and Murray. On the other hand, Castle brought out the fact that there are so many people with positive Wassermann reactions that scleroderma should be more common if it is due to syphilis. Lostorfer,[127] Brocq, Milian, Cockayne and Exchaquet [128] mentioned cases accompanied by syphilis in which the patients were not benefited by antisyphilitic treatment.

The following case of diffuse scleroderma in a syphilitic patient shows the remarkable effect of antisyphilitic treatment in some cases.

CASE 3.—*History.*—I. M. S., an American woman, aged 41, a housewife and musician, was admitted to the skin outpatient department of the Boston City Hospital, on March 25, 1927. The mother had died of tuberculosis. The father had died from an unknown cause. One brother had died of purpura hemorrhagica. One had died suddenly in infancy from an unknown cause. The husband was living and well. The patient had never been pregnant. The menstrual periods had always been regular and normal.

She had had pertussis during childhood. Trauma to the scalp in 1924 was followed by a painful scar. She had frequent attacks of tonsillitis.

The patient entered the hospital on March 25, 1927, on account of a condition of the skin and severe pain in the affected parts. Six weeks previously, she had a sore throat and cold from which she completely recovered. At that time a slight macular nonpruritic eruption was present on the backs of the hands and the lower part of the legs. Shortly after this, the patient had otitis media in the left ear, which discharged for two weeks. Three weeks before entrance, swelling and stiffness of the lips with difficulty in opening the mouth occurred rather suddenly. The stiffness spread over the face, down the neck and chest and upper back and down the arms. Severe pain preceded involvement of new areas.

Examination.—The face had a masklike expression. The shoulders were rounded forward. The arms were flexed at the elbows. The skin of the face, neck, upper arms and thorax was of a normal color and was thick, brawny, nontender and apparently edematous but not pitting. The process extended to the umbilicus, but the outlines were not sharp. Some tenderness was present beyond the borders of

123. Hillairet: De la sclérodermie, Progrès méd. **6**:793 (Oct. 6) 1878; **6**:858 (Nov. 9) 1878.

124. Lang: Arch. f. Dermat. u. Syph. **23**:526, 1891.

125. Millard: Sclérodermie améliorée par l'arrhénal, Bull. et mém. Soc. méd. d. hôp. de Paris **22**:163, 1905.

126. Milian: Bull. soc. franç. de dermat. et syph. **30**:403 (Nov. 8) 1923.

127. Lostorfer: Arch. f. Dermat. u. Syph. **23**:526, 1891.

128. Exchaquet, L.: À propos un cas de sclérodermie progressive chez un enfant, Rev. méd. de la Suisse Rom. **38**:197 (March) 1918.

the diseased area. A recent scar on the left ear drum and an old scar on the left iris were present. All movements, including mastication, were limited because of the thickened, boardlike skin. The reflexes were normal. The respiratory rate was 20.

Examination of the blood showed: hemoglobin, 80 per cent; red cells, 4,770,000; white cells, from 12,000 to 7,000; smear: polymorphonuclears, 89 per cent; lymphocytes, 4 per cent; large mononuclears, 7 per cent; eosinophils, none. A later count showed: polymorphonuclears, 46 per cent; lymphocytes, 44 per cent; large mononuclears, 7 per cent; eosinophils, 2 per cent; basophils, 1 per cent. The red cells appeared normal.

The Wassermann and Kahn tests were both strongly positive on several occasions.

Examination of the urine showed: specific gravity, 1.017; pale; acid; albumin, none; sugar, none; sediment; rare white corpuscles and epithelial cells and no casts.

Microscopic and guaiac tests of the stools gave negative results.

From deeper layers of the skin and from the underlying muscle, growths were not obtained on culture.

A specimen for biopsy was taken from the right shoulder extending deep enough to include underlying muscle. It was examined by Dr. F. B. Mallory, who reported slight inflammation (endothelial cells and lymphocytes) about the veins and hair follicles and keratosis about the mouths of the hair follicles. The muscle was normal.

The basal metabolic rate was determined six times and varied irregularly from plus 46 to minus 10. It seemed to be more affected by the pulse rate and nervousness of the patient than by any internal disturbance.

Treatment.—The patient was given antistreptococcus serum without benefit. She was also given a short course of thyroid without benefit. Large doses of bromides, cold compresses and massage were given, and active and passive motions were encouraged. When the patient was discharged to the outpatient department on June 14, 1927, little objective change in the condition of the skin had occurred, but motion was slightly more free and not painful. Administration of potassium iodide was started about this time, with slight improvement in a few days and marked benefit in six weeks. Since then, the patient had had ten injections of arsphenamine and twenty of bismuth compounds, together with the iodide.

On July 14, 1928, the Wassermann and Kahn tests were still positive. The patient did not show any signs of scleroderma except slight firmness of the skin and underlying tissues over the top of the sternum and the base of the neck by palpation. The fingers were now supple enough so that the patient was able to do her work as a pianist.

The condition was diagnosed as syphilis and diffuse scleroderma. The symptoms were relieved by antisyphilitic treatment.

COMMENT

In regard to the results of treatment for scleroderma, it is a well established fact that some patients recover spontaneously or with only local treatment such as massage and creams of various sorts (Darier [129] and Murray). Pernet [130] reported good results following ionization

129. Darier: Bull. Soc. franç. de dermat. et syph. **30**:402 (Nov. 8) 1923.
130. Pernet, G.: Scleroderma, Proc. Roy. Soc. Med. **15**:28, 1921-1922.

with zinc and massage. Weber [131] quoted a case which showed marked improvement under good food and iron iodide. Spontaneous recovery seems to be especially common in reported cases in infancy and in early childhood, particularly in the diffuse type (Jackson, Lieberthal,[132] Meyer,[133] Dolinsek [134]), but is also seen in adults (Murray). In many other cases, especially the localized forms, the lesions attain a certain size and do not extend further. In many cases, the condition goes on to atrophy and contractures with ulceration over the bony prominences without being helped by any treatment. Sclerodactylia probably never clears up spontaneously and rarely responds much to any treatment when well advanced.

However, there is a large class of both localized and diffuse cases in which the patients can be definitely helped by treatment directed to whatever underlying condition is found present after a study of the particular case, whether it is syphilis, endocrine disturbance or focal sepsis. In the patients in whom the endocrine glands are involved, some respond better to polyglandular therapy when thyroid alone has failed (Rénon [135] and Curschmann). Some require a combination of antisyphilitic and glandular treatment (Schulmann). Audry and Chatellier described a patient with cerebrospinal syphilis who improved with specific treatment. Three years later, the patient developed diffuse scleroderma with pigmentation. Arsphenamine brought about great improvement in the general condition, but no change in the skin. Then antisyphilitic treatment combined with thyroid resulted in considerable improvement in the skin which, however, progressed only to a certain degree. Ziegel reported a case of exophthalmic goiter and syphilis and fairly extensive scleroderma, in which, following two doses of arsphenamine and the administration of potassium iodide, the condition of the skin improved, the Wassermann reaction became negative, and in two months the thyroid gland had diminished in size and the symptoms of exophthalmic goiter were entirely relieved.

SUMMARY

Considering all these reports, one must admit that a large number of the cases follow infections or toxic conditions, and especially syphilis; that one or more of the endocrine glands are involved, especially the

131. Weber: Proc. Roy. Soc. Med. **12**:98, 1919.

132. Lieberthal, D.: Sclerema Neonatorum and Scleroderma, J. Cutan. Dis. **36**:29, 1918.

133. Meyer, L. F.: Ueber Sklerodermie beim Säugling, Deutsche med. Wchnschr. **45**:850 (July) 1919.

134. Dolinsek, R., and Ermenc, J.: Ueber die Sogenannte Sklerodermie der Neugeborenen, Wien. klin. Wchnschr. **38**:957 (Aug. 27) 1925.

135. Rénon, P.: Les syndromes polyglandulaires et l'opothérapie associée, Rev. gén. de clin. et de thérap. **22**:465, 1908.

thyroid, in a noticeable proportion; that a disturbance of the nervous system, sometimes the central, but more often the vegetative, is frequently present, either alone or as a result of toxemia or an infection, such as syphilis; this disturbance is sometimes accompanied, caused by or results in a dysfunction of the thyroid or other endocrine glands. Sometimes the glandular disturbance is thus apparently due in turn to syphilis or other infections, (Schulmann [136]).

The treatment must be directed to the underlying cause found after a complete medical study of the case. The prognosis is good in infants and growing children for spontaneous recovery; in adults, if the patients are seen before actual destruction of the tissues and underlying bony structures has taken place, it is often favorable if the underlying causative factors can be located and successfully treated.

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136. Schulmann, E.: La syphilis des glandes endocrines, Paris méd. **35**:442 (May 29) 1920.

DERMATITIS FROM BUTESIN PICRATE*

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We have seen no reference to butesin picrate as a cause of dermatitis in susceptible persons. It seems, therefore, worth while to call attention to the possible irritant quality which we have seen manifested in two cases. The following and most recent case is a good illustration of the accident:

REPORT OF CASE

An unmarried woman, aged 42, a ticket agent, was referred to us because of a violent attack of dermatitis. The history was as follows: A few days before, she had an attack of pain on the left side of her chest, for which a mustard plaster was applied. This produced a dry dermatitis with moderate itching, for which butesin picrate ointment was applied. The dermatitis was immediately intensified. When first seen by us a couple of days later, she had an acute weeping vesiculobullous dermatitis. It was intense over the front of the chest and neck and on the back over the scapulae, and in a less violent form involved the arms. Because of a previous experience with a similar case, the use of the ointment was immediately stopped, and wet dressings of 0.5 per cent aluminum acetate solution were applied. The dermatitis rapidly subsided. Then, under treatment with a cold cream containing zinc oxide, the dermatitis entirely disappeared. She was entirely free from it for about one week; then she put on the old dress which she had worn the first time she had applied butesin picrate ointment and which had come in contact with the ointment. Five minutes after she put on the dress, the eruption began to appear and it quickly became intense. Under the same sort of treatment, it disappeared rapidly and has not recurred.

She refused to allow a skin test with even a minute quantity of the ointment, but the sequence was so sharp and distinct between the contacts with butesin picrate and the development of the eruption that confirmatory tests seem hardly necessary to establish the direct relationship. They were so sharp in the patient's mind that she thought making a test on her would be proving the obvious. This is probably a rare accident, but two other cases, apparently of the same origin, have come to our attention.

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TULAREMIA RESEMBLING SPOROTRICHOSIS

REPORT OF A CASE *

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Tularemia may, at times, so closely resemble sporotrichosis that a differential diagnosis is impossible on clinical grounds alone. The cutaneous eruption recently observed in a patient with tularemia so definitely simulated sporotrichosis that the following report warrants recording in our dermatologic literature. Two months ago, a patient with nodular abscesses arranged in linear distribution along the dorsal surface of the forearm consulted the Dallas Medical and Surgical Clinic. At this institution a diagnosis of tularemia was made, and the case was reported to the Quarantine Division of the Dallas Board of Health. At the request of the members of this body, I saw the patient and made a tentative diagnosis of sporotrichosis or possibly an inoculation type of tuberculosis of the skin. Observation of the patient since that time, negative laboratory and therapeutic tests for sporotrichosis and a positive agglutination test for tularemia have proved the original diagnosis made at the Dallas Medical and Surgical Clinic to be correct.

REPORT OF A CASE

History.—R. M. D., a white laundryman, aged 59, consulted the Dallas Medical and Surgical Clinic on Jan. 16, 1928, concerning "sores" of six weeks' duration on the right middle finger and on the right forearm.

According to the patient's story, while hunting two months before he came to the clinic, he had dressed two cotton-tail rabbits. Five days after dressing the rabbits, he had a sudden chill, generalized aching over the body and other symptoms, which he attributed to influenza. He was confined to his home for three days at this time, but stated that he did not have fever or any definite pain except in the right axilla. A scratch, which was on the right middle finger at the time he dressed the rabbits, suddenly became swollen and painful, "as if infected." Two days later, a plug the size of a pea dropped out of the sore on his finger, and a definite ulcer formed. Two weeks after dressing the rabbits, and nine days following the chill, the ulceration on the finger spread to involve an area the size of a quarter; nodules appeared on the right forearm, and a kernel was observed in the right axilla.

Physical Examination.—The patient was first seen six weeks following the onset of the cutaneous lesions. The results of the general physical examination were essentially negative except for the eruption on the skin and the enlargement of a single gland in the right axilla. The urine contained a trace of albumin and

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* Permission to report this case was kindly granted by the Dallas Medical and Surgical Clinic.

a few granular casts. The Wassermann and Kahn reactions of the blood were negative. The white blood cells numbered 10,000 of which 59 per cent were polymorphonuclear leukocytes, 1 per cent eosinophils and 40 per cent lymphocytes. The temperature was normal, and remained so throughout the period of observation.

Skin.—The medial surface of the right middle finger presented a superficial, noncharacteristic ulceration 1.5 cm. in diameter. Extending along the dorsal surface of the right forearm, in linear arrangement from wrist to elbow, were six elevated, bluish-red, fluctuant lesions such as those depicted in figure 1. In the right axilla, a gland swollen to the size of an English walnut was hard and slightly tender to pressure (fig. 2).

Subsequent History.—A specimen of the patient's blood taken on January 16 and sent to the Hygienic Laboratory at Washington was reported to agglutinate *Bacterium tularense* in all dilutions from 1:10 to 1:640. Two days later, a slightly greenish-tinted pus was aspirated from the unruptured abscesses on the

Fig. 1.—Tularemia showing ulceration on the finger and abscesses on the back of the hand and forearm.

right forearm and planted on the various laboratory mediums. The cultures either remained sterile or produced an occasional staphylococcus. The patient was then given potassium iodide by mouth, in doses varying from 50 to 75 grains (3.25 to 4.8 Gm.) daily. The patient was subsequently observed at varying intervals.

January 27: The patient's condition was unchanged. A second specimen of blood sent to Dr. Edward Francis of the Hygienic Laboratory at Washington was again found to agglutinate *B. tularense* in all dilutions from 1:10 to 1:640.

February 8: There was no noteworthy change in the condition of the skin. The lymph gland in the right axilla, now fluctuating, had doubled in size. A piece of tissue was removed from the upper nodule on the right arm for microscopic examination.

February 10: The right axillary swelling was incised and approximately 1 ounce (30 cc.) of purulent material was evacuated. The right epitrochlear gland was moderately enlarged and tender to pressure, and the overlying skin was erythematous.

February 18: A section of skin removed ten days ago showed an essentially normal epidermis. The upper and middle thirds of the corium were slightly

edematous, with a perivascular infiltration of lymphocytes and plasma cells about the terminal arterioles. The lower third of the corium was the seat of a dense inflammatory cell exudate, including lymphocytes, plasma cells, fibroblasts and occasional polymorphonuclear leukocytes and giant cells of the Langhans and chorioplague types (foreign body types). The capillaries in this zone were few, and the lumina were narrowed from hyperplasia of their endothelial lining. Below this and entirely replacing the fatty aerolar tissue was a poorly staining necrotic mass. The microscopic picture was that of a granuloma, noncharacteristic in type.

March 6: The patient had taken from 50 to 75 grains (3.25 to 4.87 Gm.) of potassium iodide daily for the past seven weeks without apparent change in the condition of the skin. The axillary abscess still drained, and the right epi-

Fig. 2.—Tularemia showing enlarged axillary gland.

trochlear gland fluctuated on palpation. The abscesses on the forearm were incised and drained.

March 12: The lesions on the right arm had healed rapidly since incision one week before. Drainage of a mucopurulent material from the abscessed axillary and epitrochlear glands persisted. A third specimen of the patient's blood was sent to Dr. Francis for an agglutination test with the *B. tularense*. He reported: "Serum was found to agglutinate *B. tularense* in a dilution of 1:160, but not in a higher dilution. The fall in titer from 1:640, found January 21, and January 28, is a normal fall."

March 20: The skin lesions and the sinus in the right axillary region had healed. Slight drainage from the right epitrochlear gland persisted.

March 26: The patient had entirely recovered.

SUMMARY

A patient with tularemia presented a cutaneous eruption closely simulating sporotrichosis. The latter condition could not be excluded on clinical grounds alone. A final diagnosis of tularemia was made because of the repeated negative cultures for the sporothrix, the failure of the eruption to respond to large doses of potassium iodide by mouth and the positive agglutination tests of the patient's blood serum for tularemia. The subcutaneous nodules presented by this patient were highly suggestive of sporotrichosis. Subsequent necrosis of the axillary and epitrochlear lymph glands was the only clinical feature not in strict accord with such a diagnosis. Similar cases have been recorded by Hodges,[1] Permar and Weil,[2] and by Freedlander and Grossberg.[3] According to Francis, in a personal communication, subcutaneous nodules have been reported in thirty-three cases of tularemia.

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1. Hodges, F. C.: Three Cases of Tularemia, One Resembling Sporotrichosis, Am. J. M. Sc. **170**:57 (July) 1925.

2. Permar, H. H., and Weil, G. C.: The Histopathology of the Subcutaneous Lesions in Tularemia in Man, Am. J. Path. **2**:263 (May) 1926.

3. Freedlander, S. O., and Grossberg, M. H.: Tularemia, J. A. M. A. **88**:475 (Feb. 12) 1927.

LOCAL MICROSCOPIC CHANGES FOLLOWING THE ADMINISTRATION OF ANTISYPHILITIC DRUGS*

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DETROIT

The histologic changes induced by the antisyphilitic drugs at the site of injection have attracted comparatively little study, though the clinical incidence of injury is frequent and at times severe.[1]

In this study I shall attempt to record the pathologic changes induced by the three main types of antisyphilitic drugs—arsenic, mercury and bismuth—in water solutions or in oil suspensions. The experimental work was carried out on rabbits, guinea-pigs and dogs. Arsphenamine was included in this study because of a tendency to revert to its use intramuscularly,[2] though the earlier studies of Swift [3] and Kolmer [4] have called attention to its injurious action on the tissues.

EFFECT OF VARIOUS DRUGS ON THE TISSUES

Arsphenamine.—The intramuscular administration of arsphenamine is followed by an immediate severe destruction of the tissues at the site of injection (fig. 1). The necrosis of the tissues of the central portion of the area into which the drug has been injected is complete; no type of tissue escapes. The muscle fibers, the connective tissue and the nerve trunks suffer the same fate. The blood vessels are thrombosed and their walls are necrosed. Next to the central necrotic zone, there is a well demarcated zone of Zenker's necrosis, severe edema, focal hemorrhages and partly injured muscle fibers. This zone in turn is circumscribed by a zone of degenerating leukocytes in the midst of the swollen muscle fibers and severe, acute edema. The muscle fibers beyond the zone of leukocytes still show a considerable Zenker's necrosis.

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* From the Medical Research Laboratories, Parke Davis and Company, Detroit, Michigan.

1. Barthelemy, R.: Accidents locaux des injections intramusculaires de produits bismuthiques insolubles en suspension huileuse, Ann. d. mal. vén. **20**:570 (Aug.) 1925.

2. Stokes, J. H.: Arsphenamine Subcutaneously and Intramuscularly, Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1926. Richard Sutton: Intramuscular Method, Diseases of the Skin, St. Louis, C. V. Mosby Company, 1926.

3. Swift, H. F.: Absorption of Arsenic Following Intramuscular Injections of Salvarsan and Neosalvarsan, J. Exper. Med. **17**:83, 1913.

4. Kolmer, J. A.: Local Tissue Reactions by Intramuscular Injections, Principles and Practice of Chemotherapy, Philadelphia, W. B. Saunders Company, 1926.

The pathologic changes differ little, irrespective of the concentration of the solution, except that the area of necrosis increases as the concentration of the solution increases, from 0.04 Gm. to 0.3 Gm. in a volume of 1 cc. The changes occurring subsequent to the first twenty-four hours consist mainly in an attempt to repair the damage.

At the end of seven days (fig. 2) only two zones appear, the necrotic center and a newly formed connective tissue capsule. The feeble leukocyte infiltration has entirely disappeared. At the end of fourteen days (fig. 3), the necrotic center does not show any further changes. The connective tissue capsule has become more extensive and surrounds the

Fig. 1.—Arsphenamine (0.3 Gm.) was administered in 1 cc. of water. The muscle, a rabbit's lumbar muscle, was excised at the end of forty-eight hours. The lesion presents a diffuse, coagulation necrosis of all structures and a mild leukocyte invasion of its periphery.

injured area like an iron ring, from the one side, preventing the escape of the liquefied necrotic material, and, from the other side, shutting off the nutrition to the uninjured muscle, causing the latter to undergo autolysis and to gather their nuclei in clumps. The process of encapsulation and autolysis of the muscle fibers inside of the capsule proceeds until all the muscle fibers have been absorbed and displaced by the connective tissue. At the end of two weeks new blood vessels appear in the capsule, and fenestration of some of the larger thrombosed blood vessels takes place.

Fig. 2.—Arsphenamine (0.04 Gm.) was administered in 1 cc. of water. The muscle was excised on the seventh day. The central portion of the lesion is made up of necrotic liquefying material. The peripheral zone shows autolyzing muscle fibers, lime salt deposits and new fibrous tissue formation.

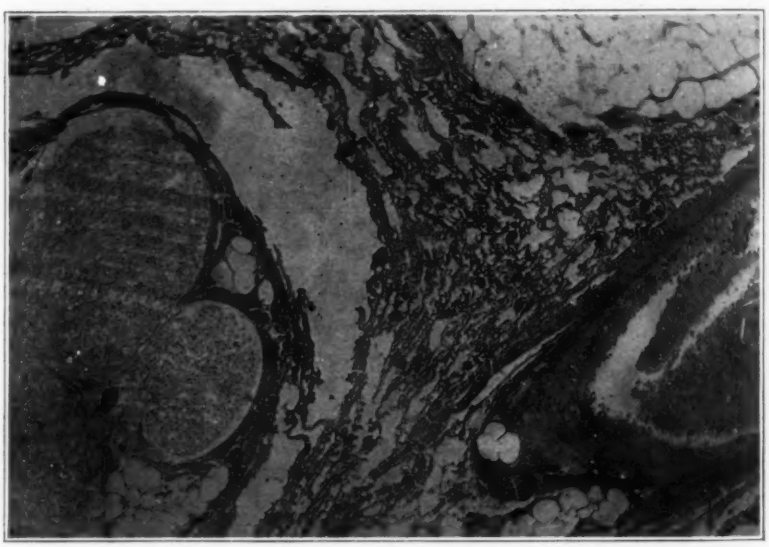

Fig. 3.—Arsphenamine (0.045 Gm.) was administered in 1 cc. of water. The muscle was excised on the fourteenth day. The illustration shows the central portion of the lesion; liquefaction, necrotic nerve fibers and necrotic, thrombosed vessels are present.

The process of encapsulation and autolysis of the muscle fibers (fig. 4) remains active at the end of three weeks. The only difference noted at the end of this period is an extensive fenestration of some of the thrombosed blood vessels and the formation of new blood vessels in the capsule. This process appears to be at its height at the end of three weeks.

At the end of five weeks the necrotic central area appears as a multilocular cyst (fig. 5) surrounded by a thick, contracting fibrous capsule. The trabeculae of the cyst consist of the necrotic connective tissue fasciculi. As the capsule contracts, the newly formed blood vessels in the

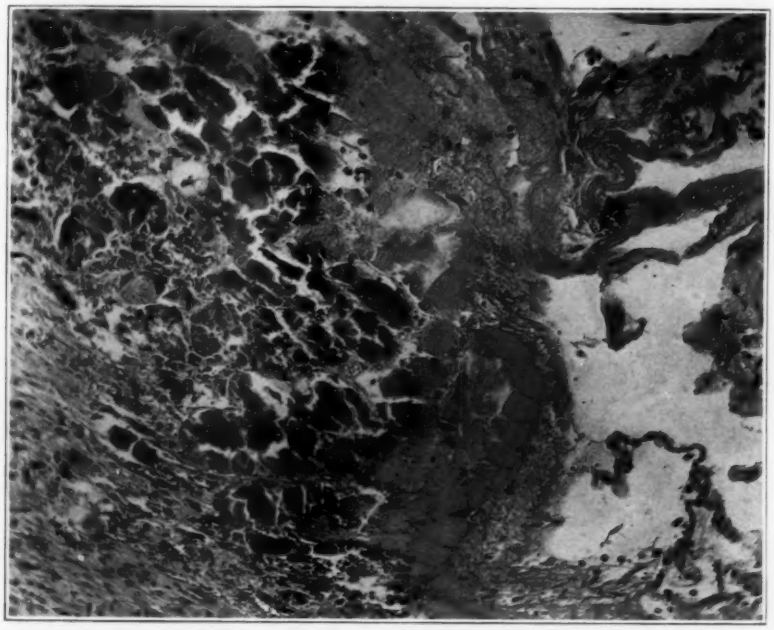

Fig. 4.—Arsphenamine (0.040 Gm.) was administered in 1 cc. of water. The muscle was excised on the twenty-first day. The central necrotic area has the appearance of a multilocular cyst. The periphery shows an extensive fibrous capsule, degeneration and lime salt deposit in the muscle fibers.

capsule become entirely obliterated and hemosiderin is deposited in the sclerotic tissues. In five weeks, the degree of healing has been negligible. It is apparent that a great number of weeks would pass before a quiescent scar would form.

Neoarsphenamine.—The injection of 0.3 and 0.45 Gm. of neoarsphenamine in the muscle causes, in twenty-four hours, necrosis of the muscle fibers and the connective tissue fasciculi. The necrosis is accompanied with an acute edema, multiple hemorrhages and thrombosis of the blood vessels (fig. 6). A slight leukocyte infiltration appears

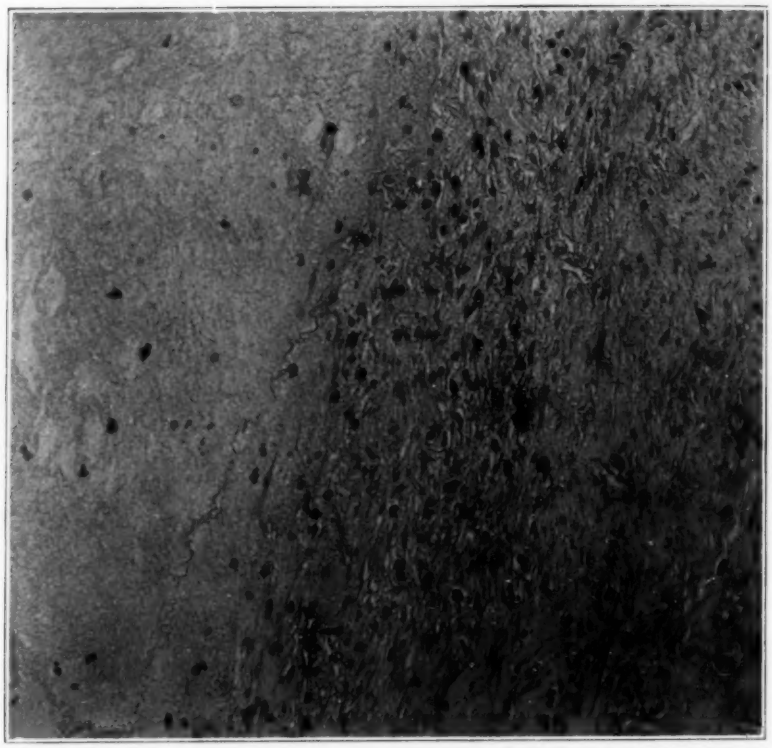

Fig. 5.—Arsphenamine (0.04 Gm.) was administered in 1 cc. of water. The muscle was excised on the thirty-sixth day. The central area presents a necrotic multilocular cyst surrounded by a thick sclerotic capsule showing obliteration of the blood vessels and a deposit of hemosiderin.

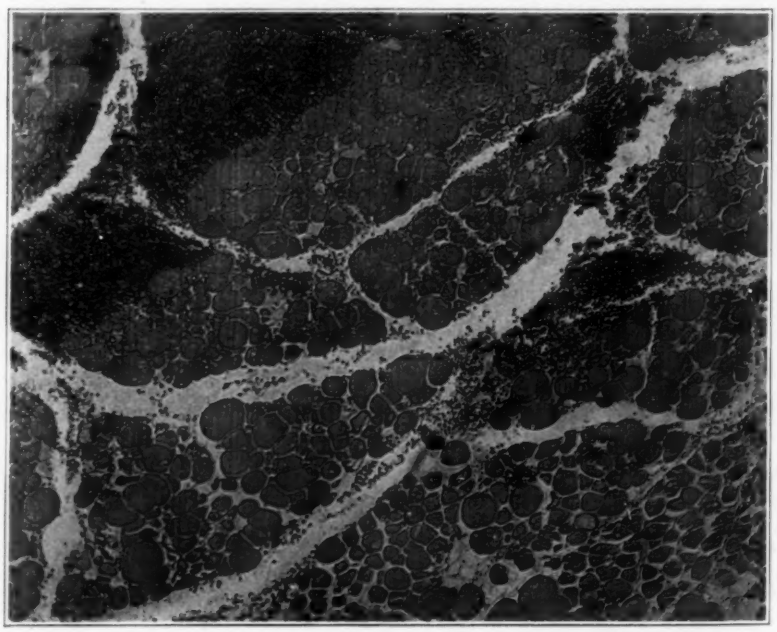

Fig. 6.—Neoarsphenamine (0.45 Gm.) was administered in 1 cc. of water. The muscle was excised at the end of twenty-four hours. The area of injection shows coagulation necrosis, multiple hemorrhages and acute edema.

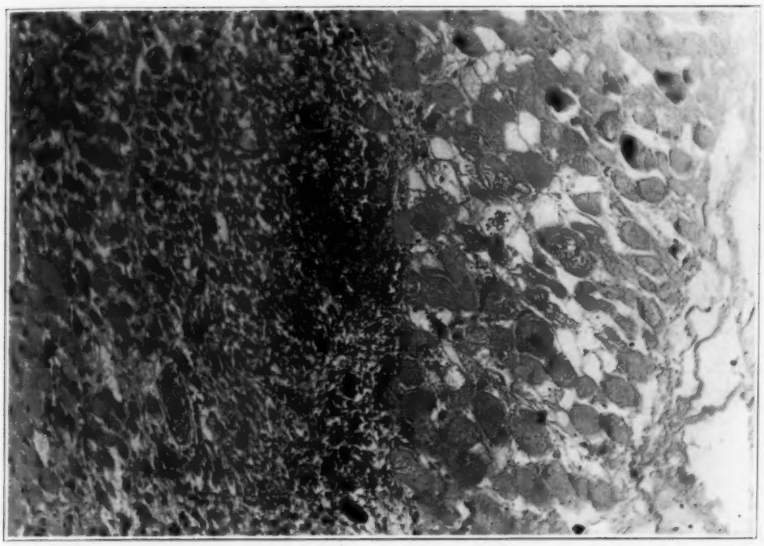

Fig. 7.—Neoarsphenamine (0.04 Gm.) was administered in 1 cc. of water. The muscle was excised on the seventh day. The central portion is entirely necrotic. The periphery shows autolysis of the muscle fibers, lime salt deposits and extensive fibrous capsule formation.

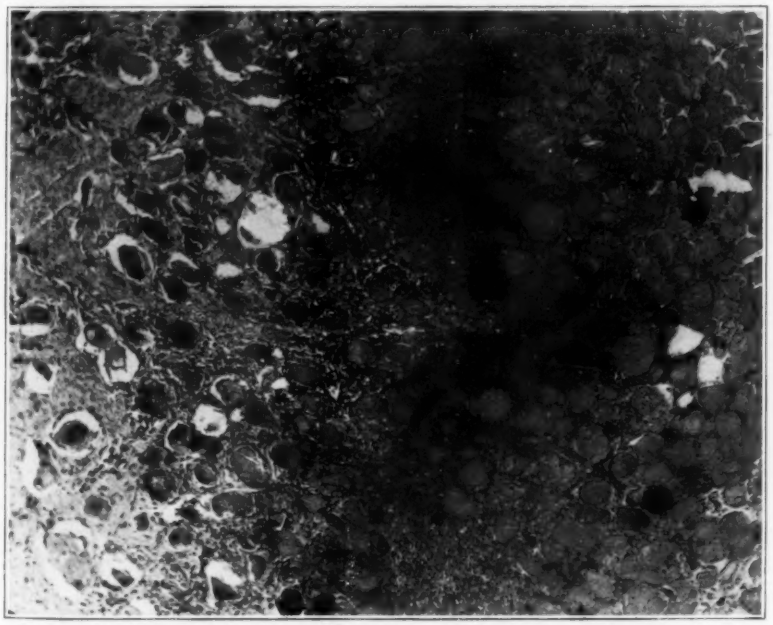

Fig. 8.—Neoarsphenamine (0.3 Gm.) was administered in 1 cc. of water. The muscle was excised on the twenty-eighth day. The lesion shows an extensive necrotic center, a zone of disintgerating leukocytes, autolyzing muscle fibers, lime salt deposits and a formidable connective tissue capsule.

around the periphery. The ninety-six hour specimen differs little from the twenty-four hour one. Some of the necrotic muscle fibers have been autolyzed, and some show fatty degeneration with a lime salt formation. At the end of seven days, a definite encapsulation of the necrotic area occurs followed by liquefaction necrosis of the necrotic and slightly injured muscle fibers (fig. 7). By the end of two weeks, the connective tissue capsule is of considerable thickness. The liquefaction necrosis is extensive and considerably more widespread as compared with that caused by arsphenamine. The fenestration of the capsule occurs earlier also and is considerably more extensive. At the end of three weeks, the connective tissue capsule begins to contract and

Fig. 9.—Neoarsphenamine (0.3 Gm.) was administered in 1 cc. of water. The muscle was excised on the twenty-eighth day. The lesion appears as a sterile abscess containing necrotic tissue elements.

the newly formed blood vessels become obliterated with a deposit of hemosiderin. The healing process is especially evident at the end of five weeks in the case of an active muscle. The pathologic changes, however, are not distinctly uniform. In the case of injections into the active muscle of the thighs, the healing effect appears more rapid and is not, as a rule, associated with as considerable an injury and infiltration as compared with the results of injection into a passive lumbar muscle. The injury to a passive lumbar muscle from an injection of neoarsphenamine appears to be just as severe as that resulting from arsphenamine. At the end of four weeks, a muscle into which such an injection is made shows a necrotic center surrounded with a zone of disintegrated leukocytes, necrotic, autolyzing muscle fibers, areas of round cell infiltration

Fig. 10.—Neoarsphenamine (0.3 Gm.) was administered in 1 cc. of water. The muscle was excised on the forty-second day. The lesion shows a large central necrotic area, autolyzing muscle fibers, lime salt deposit and an extensive fibrous capsule.

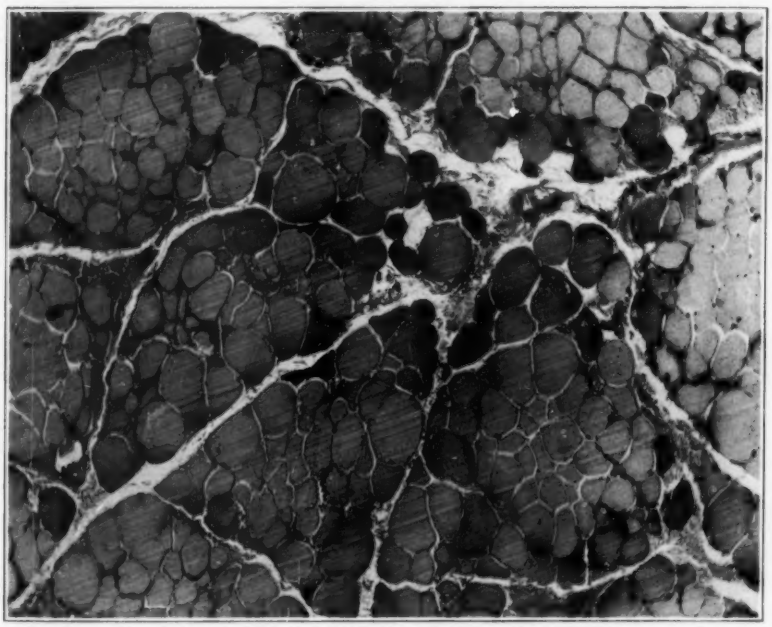

Fig. 11.—Silver arsphenamine (0.3 Gm.) was administered in 1 cc. of water. The muscle was excised at the end of forty-eight hours. Necrosis of the connective tissue trabeculae and of the adjacent muscle fibers is shown; also focal hemorrhages and thrombosis of the blood vessels. Silver is precipitated into the tissues.

and a fibrous capsule formation around the periphery (fig. 8). Figure 8 shows a section of the lesion under high power, and figure 9 shows the whole lesion under low power.

The healing of the injury due to neoarsphenamine is slight at the end of six weeks. When the injection is given into an active muscle of the thigh, the improvement is more noticeable at this time. Yet, as a whole, little improvement has taken place, except that the edema has subsided and that the injured area is definitely surrounded with a dense fibrous tissue. The area of injection itself remains entirely necrotic (fig. 10).

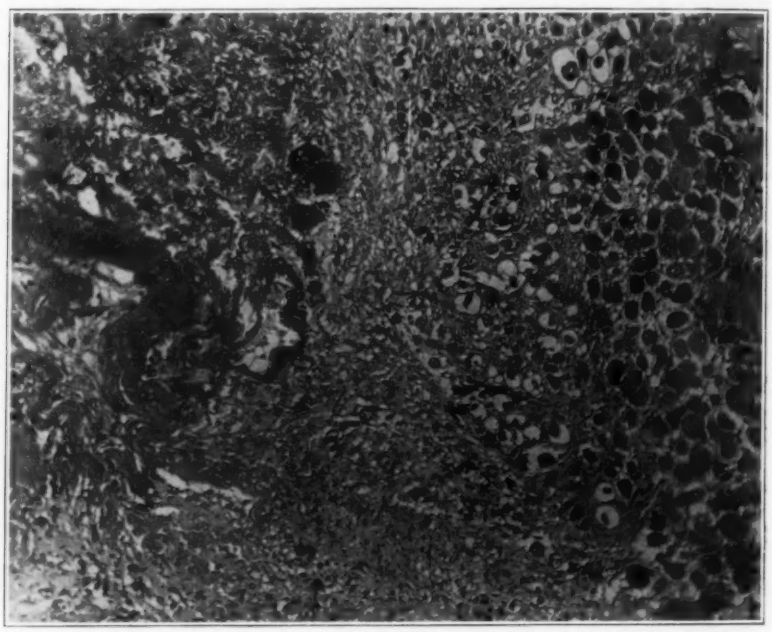

Fig. 12.—Silver arsphenamine (0.045 Gm.) was administered in 1 cc. of water. The muscle was excised on the fifteenth day. There is a large central necrotic area surrounded by disintegrating muscle fibers and a newly formed connective tissue capsule.

Silver Arsphenamine.—The administration of silver arsphenamine deep into the muscle causes an immediate severe destruction of the connective tissue trabeculae. To a lesser degree, the injury extends to the muscle fibers adjoining the path of the flow of the injected solution (fig. 11). The blood vessel walls are necrosed, and the contents thrombosed. The silver of the compound is precipitated at the site of the injection. As the inoculum diffuses from the site of injection, considerable injury occurs to all structures farther removed from the center of the area of injection. In general, the lesion is associated with

an acute edema, necrosis of the muscle fibers, hemorrhage and thrombosis of the blood vessels. On the whole, the initial injury is not as severe as in the case of injections of arsphenamine or neoarsphenamine. At the end of the first week, the reparatory process is in full progress, and the extent of the injury can be properly estimated only at this time. Indeed, the degenerative, autolytic changes disclose the severe toxic nature of the silver arsphenamine on the tissues. The center of the area of injection is entirely necrotic; the injured muscles undergo autolysis, atrophy and lime salt deposition. There is a severe edema throughout. The nerve trunks become necrotic. Blood vessels show

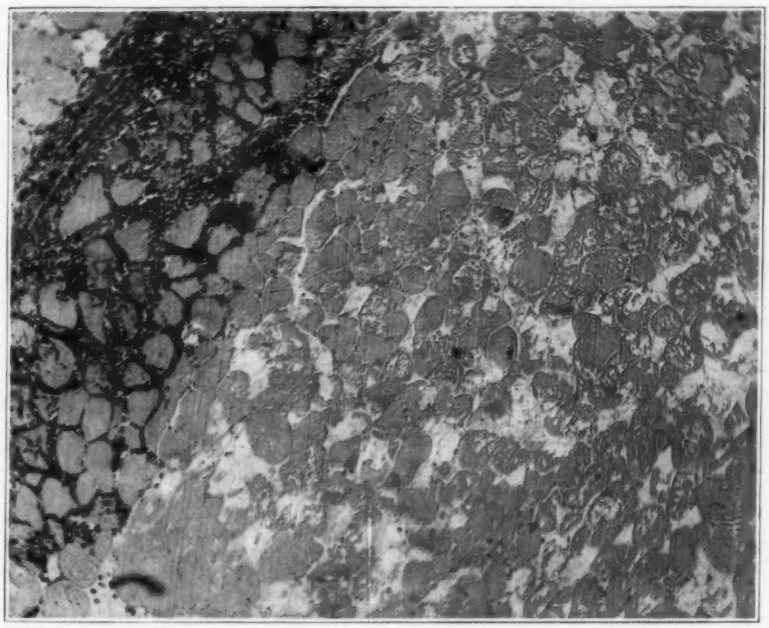

Fig. 13.—Sulpharsphenamine (0.45 Gm.) was administered in 1 cc. of water. The muscle was excised at the end of forty-eight hours. The lesion presents extensive necrosis of the muscle fibers, connective tissue, blood vessels and nerve trunks. Acute edema and leukocyte invasion of the periphery of the lesion is also shown.

extensive thrombosis and necrosis. In fact, the injury is just as severe as in the case of injections of neoarsphenamine. Leukocytosis plays a minor rôle, and leukocytes that penetrate to the injured tissues become autolyzed. The necrotic area and the injured tissues are surrounded by an extensive fibrous capsule (fig. 12).

The pathologic changes at the end of two weeks remain the same as at the end of seven days, except that the connective tissue capsule is more formidable and begins to show the constricting and strangulating effect. The newly formed blood vessels are being obliterated with a

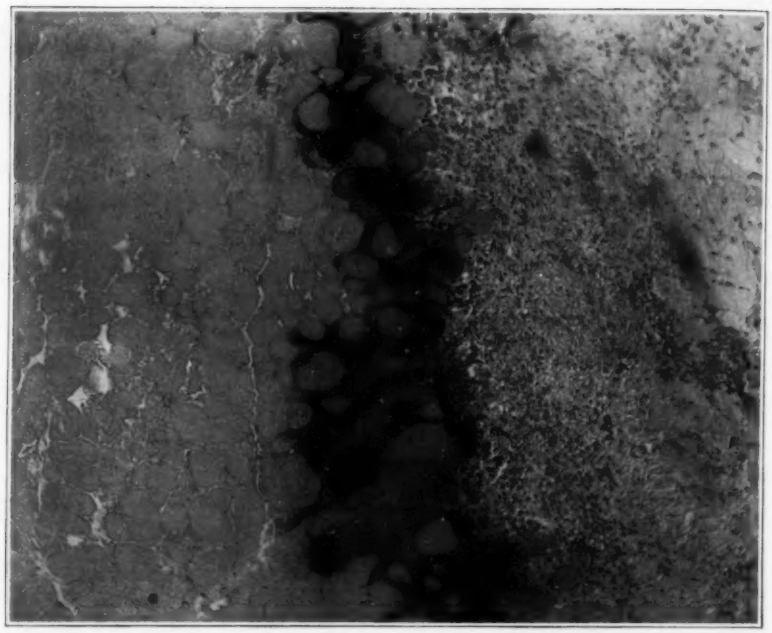

Fig. 14.—Sulpharsphenamine (0.39 Gm.) was administered in 2.5 cc. of water. The muscle was excised on the thirtieth day. The lesion presents a central necrotic area of coagulation necrosis. The periphery shows autolyzing leukocytes and an extensive fibrous capsule.

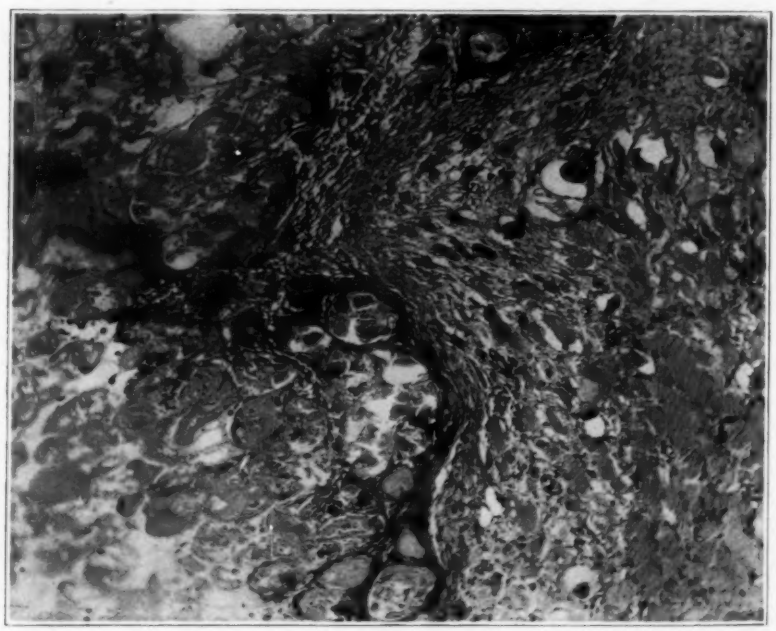

Fig. 15.—Sulpharsphenamine (0.39 Gm.) was administered in 2.5 cc. of water. The muscle was excised on the fifty-seventh day. The central necrotic area shows partial lysis of the muscle fibers. The periphery presents degenerating muscle fibers with lime salt deposit and a thin fibrous capsule.

deposit of hemosiderin in the tissues, while the necrotic tissues are gradually autolyzed and the lesion acquires the appearance of a cyst.

Sulpharsphenamine.—The acute injury from an injection of sulpharsphenamine manifests itself in an acute, severe edema and necrosis of the muscle and connective tissues. The necrosis of the muscle appears somewhat less extensive in comparison with that caused by neoarsphenamine, yet the injury is extremely grave. In the initial stage, the main difference from the effects produced by neoarsphenamine consists in a persistent attempt of leukocyte infiltration around the periphery of the lesion (fig. 13).

A similar leukocyte infiltration is noticed around the injured blood vessels and in their walls; however, this leukocyte walling off lasts only

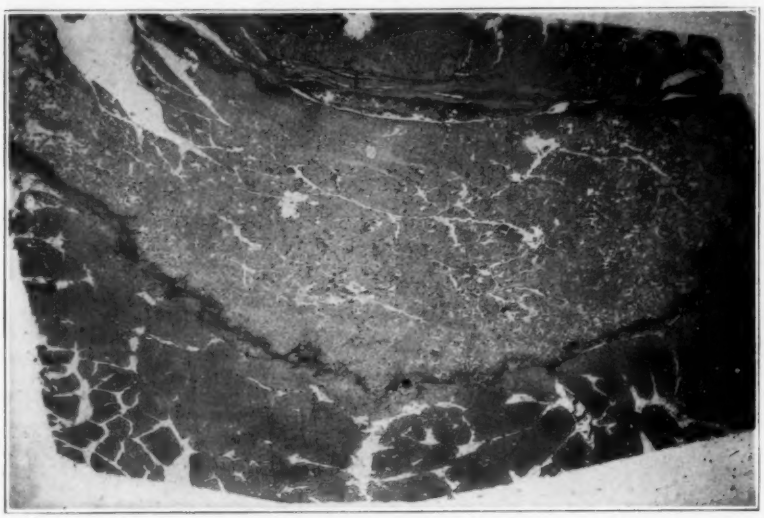

Fig. 16.—Sulpharsphenamine (0.39 Gm.) was administered in 2.5 cc. of water. The muscle was excised on the fifty-seventh day. The same lesion is shown as in figure 15, but under a low power magnifying lens showing the whole lesion. It is essentially a sterile abscess showing little or no healing at the end of eight weeks.

a brief time. The leukocytes become lysed, and a connective tissue capsule is in full evidence at the end of the seventh day.

Specimens taken four and eight weeks, respectively, after an injection of this drug reveal an almost unbelievable injury (fig. 14). The central area of the site of injection is entirely necrotic, and the tissue elements have undergone slight resolution, i. e., the necrotic tissues have not undergone autolysis. The periphery of the large necrotic area is surrounded with a zone of fragmented leukocytes, which is, in turn, surrounded by a zone of thin connective tissue capsule. This histologic

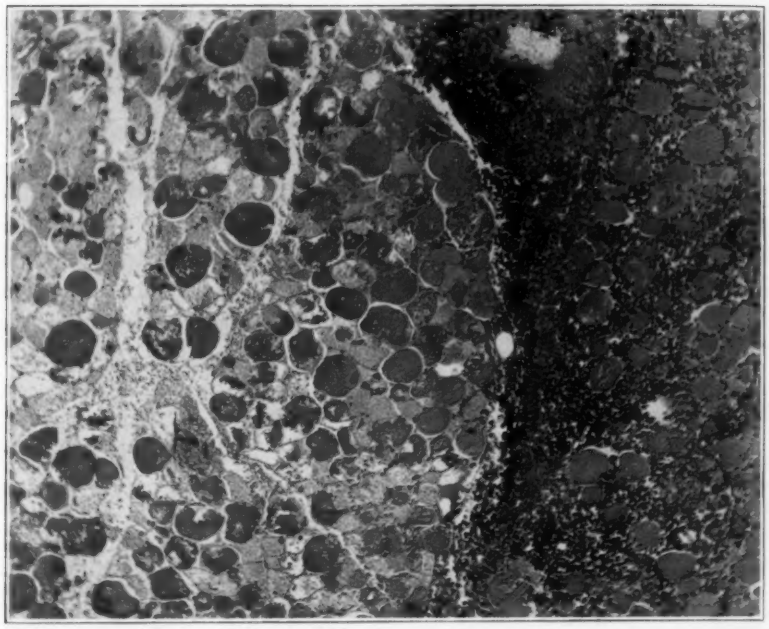

Fig. 17.—Mercuric salicylate (0.13 Gm.) was administered in 1 cc. of oil. The tissues were excised at the end of seventy-two hours. Acute edema and necrosis of the central part of the area of injection are present. The periphery shows massive leukocyte infiltration and lysis of the muscle fibers in the midst of the proliferating fibroblasts.

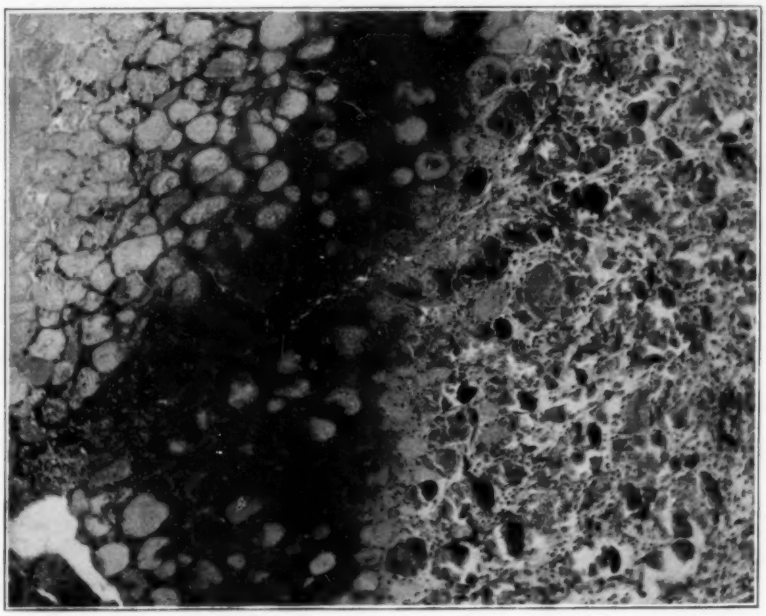

Fig. 18.—Mercuric salicylate (0.13 Gm.) was administered in 1 cc. of oil. The tissues were excised at the end of seven days. The periphery of the lesion shows extensive new fibrous tissue formation and lime salt deposit in the degenerating muscle fibers. Centrally to the fibrous capsule, an extensive zone of leukocytes and a central necrotic area are seen.

picture of the lesion shows little or no change at the end of eight weeks (figs. 15 and 16) as compared with that of four weeks. The work was not carried out further because the comparative microscopic study of the essential arsphenamine derivatives indicated that the injury from sulpharsphenamine appeared just as severe and just as extensive as that from neoarsphenamine.

The microscopic changes induced by these studies on arsphenamines are extremely severe. The essential lesion is a sterile abscess encysted

Fig. 19.—Mercuric succinimide (0.005 Gm.) was administered in 0.5 cc. of water. The tissues were excised at the end of seven days. The lesion presents an extensive necrotic central area with a fibrous capsule on the periphery.

in a formidable connective tissue capsule. In the process of repair, the connective tissue capsule aggravates further the degree of injury by cutting off the exchange of substances between the contents of the capsule and the surrounding normal tissue. In time, the contents of the capsule undergo autolysis with a formation of a multilocular cyst.

In these experiments of eight weeks' duration, it was noted that the lesion in the active muscle healed more rapidly than that in the passive muscle. Neoarsphenamine and sulpharsphenamine appeared equally

irritating to the tissues; both produced severe necrosis of all tissue structures at the site of injection.

Mercury.—In a similar manner, a number of mercurial compounds were studied. The existence of a large number of mercurial preparations necessitated the selection of a few typical preparations.

Mercuric salicylate in olive oil was selected to represent the insoluble compounds. Mercuric iodide, succinimide, cyanide, benzoate, and thiobenzoate were selected to represent the water-soluble preparations.

When injected deep into the muscle, mercuric salicylate in oil produces in three days severe destruction of the tissues at the site of injec-

Fig. 20.—Water-soluble but tissue-insoluble bismuth tartrate (0.09 Gm.) was administered in 1 cc. of water. The tissues were excised at the end of forty-eight hours. The bismuth has been precipitated by the tissues and the tissue fluids in the connective tissue fasciculi, between the muscle fibers. All tissue structures are entirely necrotic.

tion (fig. 17). In the midst of an acute edema the muscle fibers show all stages of degeneration, from the mild Zenker's necrosis, fatty degeneration and cloudy swelling to a frank necrosis. At this stage, the mercury is still present in the tissues but enclosed in an envelop of coagulated protein. The periphery of the injured area is actively invaded by leukocytes which, in part, undergo lysis. The full scope of injury is best noted at the end of seven days. What appears in three days to be a partial injury reveals complete necrosis at the end of seven

days (fig. 18). The reparatory fibroblastic encapsulation of the injured area tends to increase the injury further. When the connective tissue proliferates between the injured muscle fibers, the latter become strangulated and undergo degeneration with a considerable lime salt deposit. At the end of two weeks, the fibrous capsule has become enormously thick and the leukocyte invasion has become more pronounced, actually simulating an abscess. The lesion recedes slowly because the sclerotic capsule considerably delays the absorption of the necrotic tissues. Healing takes place by the gradual absorption of the necrotic tissues and the formation of a connective tissue scar. The healing process is more rapid in

Fig. 21.—Water-soluble, tissue-soluble bismuth thioglycollate (0.2 Gm.) was administered in 1 cc. of water. The tissues were excised at the end of twenty-four hours. The lesion presents an acute edema, Zenker's necrosis and a few necrotic muscle fibers. Bismuth was not precipitated in the tissues.

muscles during exercise than in muscles at rest. A quiescent scar following the administration of mercuric salicylate may result at the end of from three to four months.

The injury from the administration of soluble mercury compounds differs little from that caused by insoluble salts. Intramuscular injection of soluble mercury compounds produces necrosis of all tissue elements. This is followed by a leukocyte invasion, fibrosis and finally a scar tissue formation. The soluble compounds differ somewhat in their acute respective manifestations; thus mercury thiobenzoate appears less

destructive than mercury cyanide and the latter is less destructive than the mercuric iodide or succinimide (fig. 19). The subsequent changes are in the main the same, namely, fibrosis with a quiescent scar tissue formation.

In summary, the injection of soluble mercurial drugs intramuscularly produced severe edema and necrosis of tissues at the site of injection. The acute lesion was followed by a leukocyte infiltration and the formation of a connective tissue capsule. Healing took place by fibrous tissue formation, and considerable time ensued before a quiescent scar was produced.

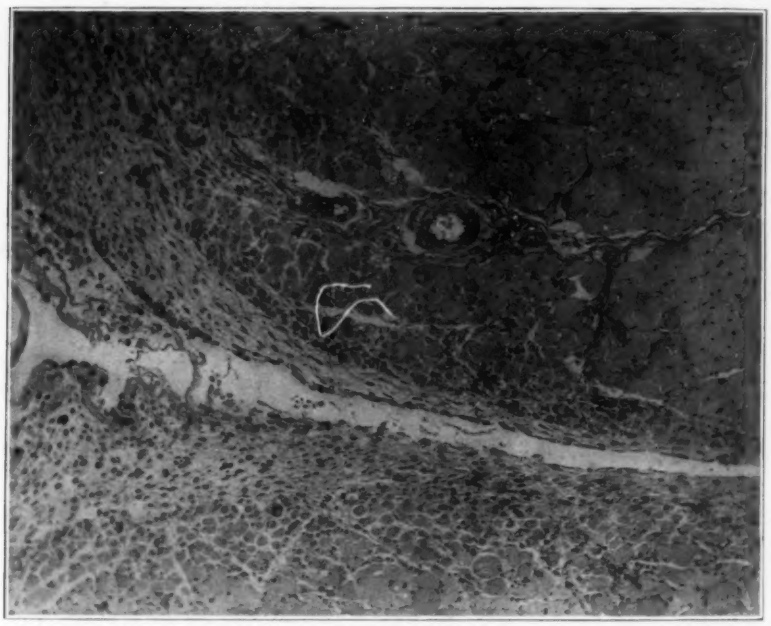

Fig. 22.—Water-soluble, tissue-soluble bismuth thioglycollate (0.2 Gm.) was administered in 1 cc. of water. The tissue was excised at the end of seven days. The site of injection presents young connective tissue scar. Unusually rapid healing of the injured tissues resulted.

Bismuth Preparations.—In the case of bismuth preparations, one encounters pathologic changes more or less specific to each type of compound and according to their relation to the tissues at the site of injection they may be classed as follows: (1) the water-soluble but tissue-insoluble preparations, (2) the water-soluble and tissue-soluble preparations, (3) the insoluble salts, oil or water suspensions, and lastly, (4) the metallic bismuth, water or oil suspensions.

The water-soluble but tissue-insoluble bismuth preparations are changed into insoluble preparations on reaching the tissues or tissue

juices when injected as water solutions or as oil suspensions. To this group belong the majority of inorganic bismuth salts, as tartrates, citrate, gallates, etc.

The injected water-soluble bismuth tartrate is precipitated by the tissues and is distributed along the connective tissue fasciculi of the muscle bundles (fig. 20). The tissues in contact with the preparation become necrosed. The absorption of the precipitated bismuth takes place as if an insoluble bismuth preparation had been injected, namely, the

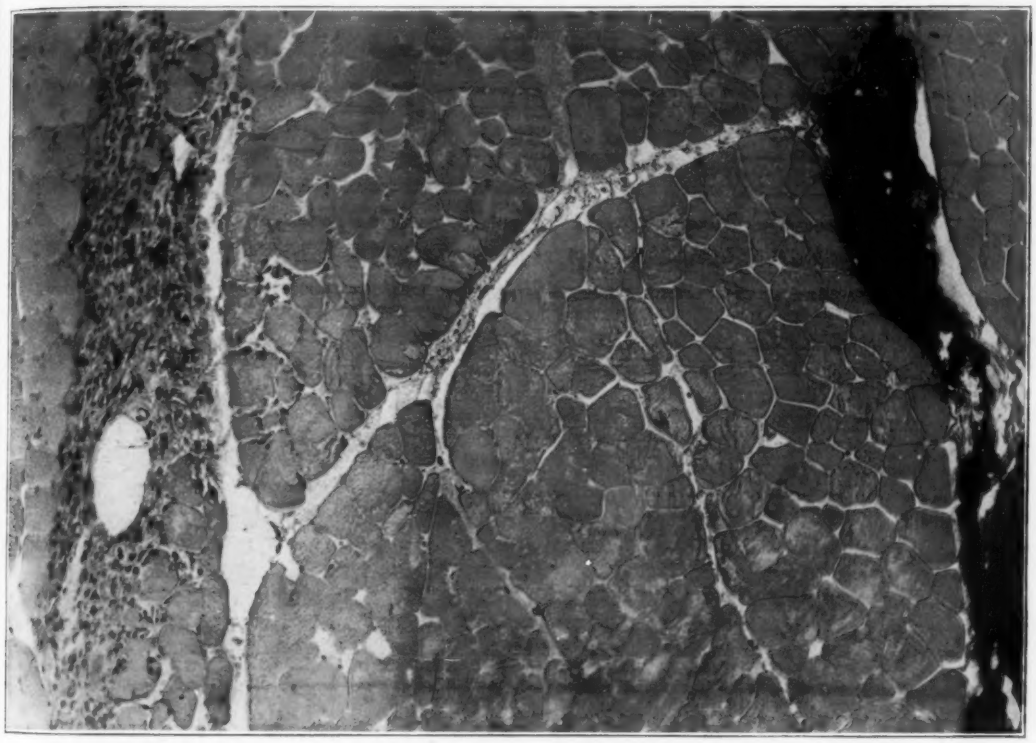

Fig. 23.—Bismuth salicylate (0.13 Gm.) was administered in 2 cc. of oil. The tissues were excised at the end of seven days. The injected bismuth lies in direct contact with the muscle fibers. Zenker's necrosis of the muscle fibers is due to the presence of creosote and camphor in the preparation. A fibrous capsule surrounds the area of injection.

bismuth has to be dissolved first. The injury is somewhat less extensive in the case of injections of bismuth citrate, but the healing process is the same.

The repair of the tissues occurs on similar lines, as in the case of mercuric salicylate. The injured area is surrounded by a zone of fibrosis. A feeble leukocyte infiltration occurs; in ten days, this is

followed by a connective tissue capsule formation. Once encapsulated, the necrotic area resolves slowly, and weeks ensue before a quiescent scar results.

The water-soluble and tissue fluid-soluble preparation of bismuth thioglycollate (thio-bismol) differs strikingly in two respects from the remaining bismuth compounds. First, it remains soluble when injected into the tissues. Second, the pathologic changes induced are minimal. In my previous studies,[5] it was brought out that this

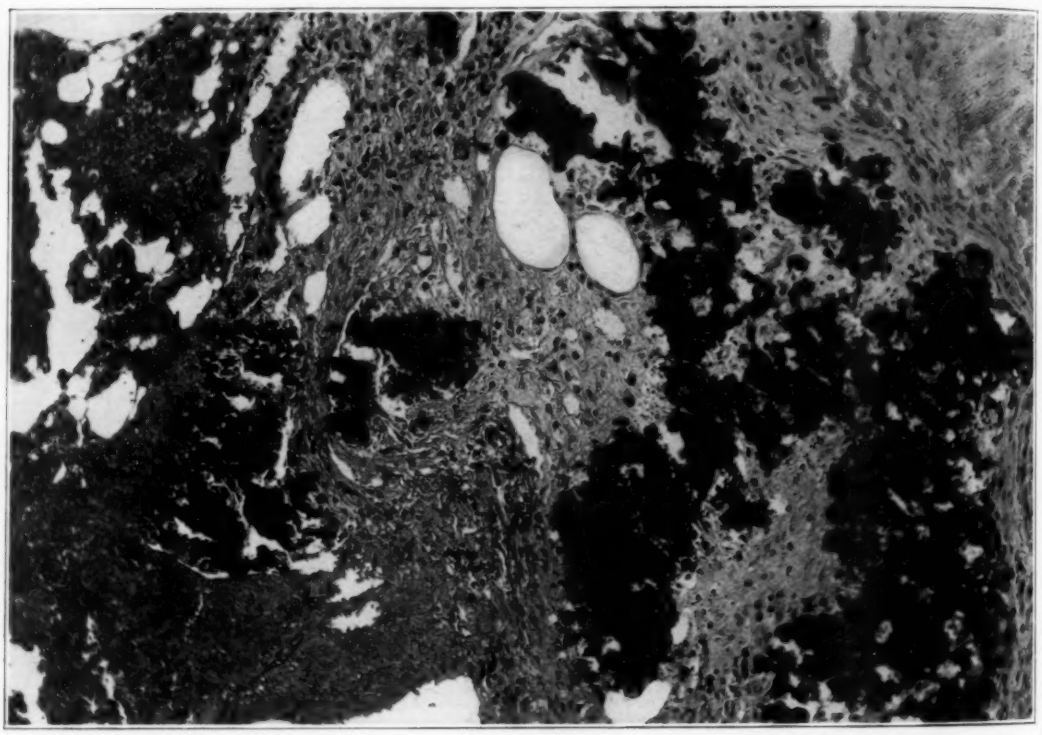

Fig. 24.—Bismuth salicylate (0.13 Gm.) was administered in 2 cc. of water. The tissues were excised at the end of twenty-seven days. Extensive lime salt deposits, caseating necrosis, oil lakes and fibrous capsule formation resulted. Bismuth was not found in the tissues.

type of compound diffuses out of the site of injection in less than two hours. Because of the high concentrations injected (1 cc. of a 20 per cent solution), a few muscle fibers appear necrosed and some show Zenker's necrosis. There is a certain amount of edema through the area of injection (fig. 21). The injection of

5. Gruhzit, O. M., and Sultzaberger, J. A.: Bismuth Absorption; Distribution and Elimination, Am. J. Syph. **11**:103, 1927.

bismuth thioglycollate is not associated with an infiltration of the injured area with leukocytes. The necrotic muscle undergoes autolysis, and the partly injured muscles rapidly undergo atrophy. At the end of the seventh day following the injection, there is a rapid proliferation of fibrous tissue, and the injured tissues have been entirely displaced by young connective tissue (fig. 22). At the end of two weeks, the fibrous elements become more abundant and of a more mature appearance. The whole area thus affected is only about 1 mm. in thickness and about 6 mm. in length. At the end of three weeks, the

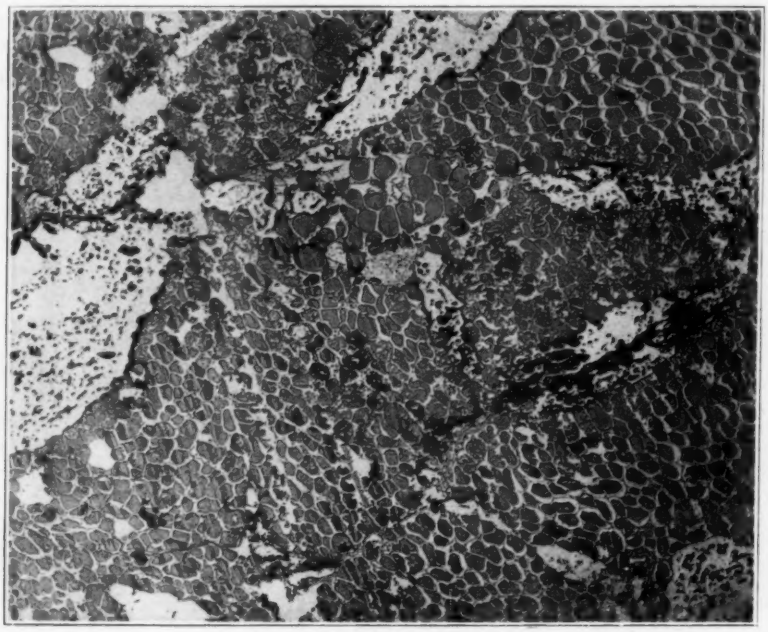

Fig. 25.—Bismuth tartrate (0.10 Gm.) was administered in 1 cc. of oil. The tissues were excised at the end of seven days. The lesion presents a complete necrosis of the area of injection, acute edema and effusion of the tissue fluids around the injected bismuth masses. Bismuth remained floating in the tissue fluids for from ten to fourteen days. Effusion occurred at the end of this period. Absorption took place in the same manner as other insoluble bismuth salt preparations.

hyperplasia of the connective tissue begins to recede, and the injured area passes into a stage of quiescent scar.

An injection of insoluble salts in water or oil suspensions produces pathologic changes at the site of injection peculiar to each preparation. In the case of bismuth salicylate suspended in olive oil in the presence of 10 per cent of creosote and 10 per cent of camphor, the injected

bismuth lies in direct contact with the muscle fibers. Eight days following an injection the muscle fibers show considerable Zenker's necrosis (fig. 23). A fibrous capsule has already far advanced. Beyond the capsule normal muscle is found. A somewhat different picture is seen if the bismuth salicylate is injected in a water suspension. At the end of five days, the site of injection shows considerable necrosis with lime salt deposits, Zenker's necrosis and edema. It appears that more destruction results to the tissues from the injection of water suspensions

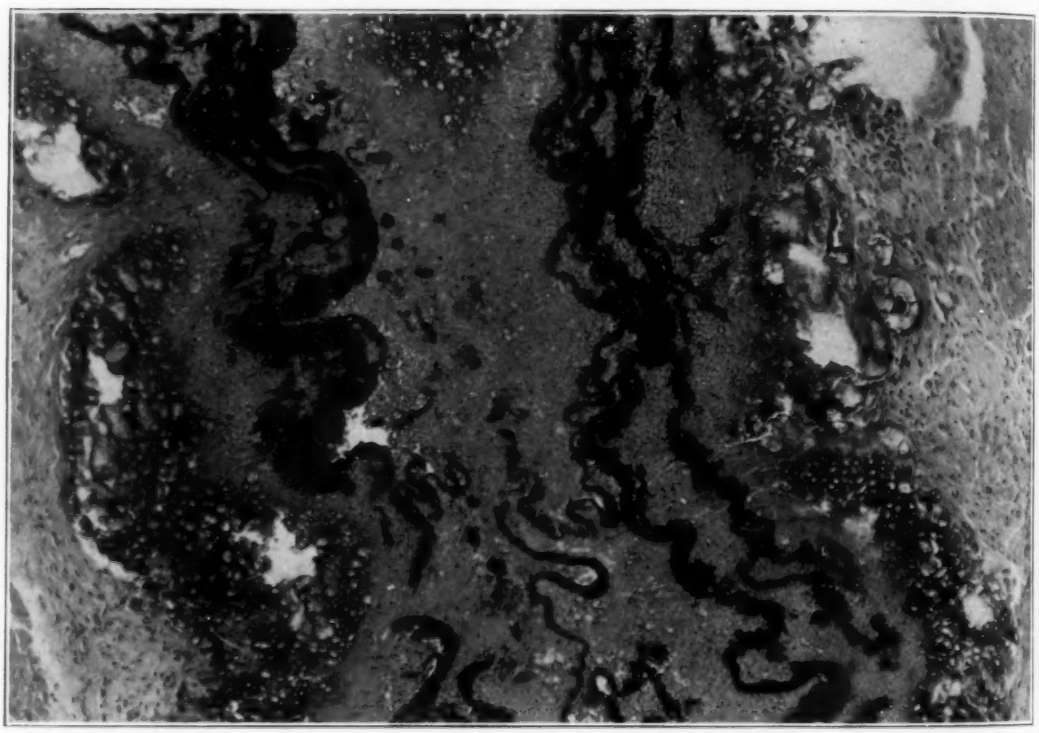

Fig. 26.—Metallic bismuth suspension in dextrose solution (0.10 Gm.) was administered in 1 cc. of water. The tissues were excised at the end of fifty-four days. The periphery of the lesion is surrounded with a heavy fibrous capsule. Centrally to it is an irregular zone of calcium deposits. In the midst of a caseating material the bismuth remains unabsorbed.

than from oil suspensions of bismuth salicylate. At the end of four weeks (fig. 24), the site of injection from an oil preparation represents a fibrous mass enclosing lime salt deposits and a caseating material. In time, the muscle fibers are autolyzed and displaced by connective tissue. A leukocyte or other cell infiltration is almost uniformly absent. From the study of the histologic changes at the site of injection, it is apparent that the absorption of the insoluble bismuth

salts must be looked on as a process of dissolution and diffusion of the soluble products rather than an absorption by leukocytes or other wandering cells.

The pathologic changes due to the injection of bismuth tartrate in oil differ from those of bismuth salicylate, at least in the initial stages. An injection of bismuth tartrate in oil results in a severe necrosis of the tissues (fig. 25). This is further complicated with a severe infusion of tissue fluids in the areas containing the salt. The surrounding tissues appear shrunk and dehydrated, while the bismuth-containing areas become distended. This process lasts for about the first ten to fourteen days, then a gradual absorption of the liquid takes place, and, with the absorption of the infiltrated fluid, the precipitated bismuth is gradually redissolved and diffused. From the third week on, considerable fibrosis, calcification and caseation take place. The process of healing is more protracted than it is after the injection of bismuth salicylate.

The injection of metallic bismuth in water suspensions produces less immediate injury than the injection of oil suspensions of bismuth salts. The subsequent changes, however, differ little from those caused by other bismuth preparations. The absorption of metallic bismuth is extremely slow. Its presence in the tissues leads to fibrosis, encapsulation and necrosis of the encapsulated tissues. At the end of fifty-four days (fig. 26), the injected metallic bismuth is surrounded by a fibrous capsule and shows extensive lime salt deposits and caseating masses.

CONCLUSIONS

From this study of pathologic changes induced in animals, at the sites of injection of the main types of antisyphilitic drugs, it appears that the administration of the arsphenamine type of drugs intramuscularly invariably results in the formation of sterile abscesses, the healing of which is comparatively slow. At the end of eight weeks, the healing has shown little progress. In this respect, sulpharsphenamine causes just as extensive an injury as neoarsphenamine. The mercury compounds produce the same type of injury only in a lesser degree. The injured areas, however, are more rapidly absorbed and fibrosed, especially when mercury thiobenzoate, benzoate and cyanide are used. The ultimate result is a scar tissue at the site of injection.

The bismuth compounds cause local injury according to the degree of their corrosiveness. The least injury is produced in the case of water-soluble, tissue-fluid soluble compounds, such as bismuth thioglycollate. The bismuth compounds suspended in oil or water cause considerable local necrosis, which is usually followed by the formation of a sterile abscess. The absorption of the necrotic material with the

formation of a scar is a prolonged process. This, however, occurs more readily in the muscle under constant exertion than in an inactive muscle.

Bismuth thioglycollate, a water-soluble and tissue-fluid soluble preparation, causes the least injury to the tissues at the site of injection and is followed by a most rapid healing of the lesion.

The tissue-fluid insoluble bismuth preparations must first be dissolved by the tissue fluids before they can be absorbed. Phagocytic action, if present, appears to be of minor importance.

LYMPHANGIECTATIC CYST OF THE LEFT LABIUM MINUS

REPORT OF A CASE *

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Cysts of the vagina are by no means uncommon. The presence of a congenital benign cystic neoplasm in the labium minus, however, is unusual and interesting. The American literature contains a dearth of such reported cases. Dr. Fredrick J. Taussig [1] stated that, "Neoplastic cysts of the vulva are extremely rare." Included in this statement are such rare conditions as tumors of the sweat glands, mucous cysts, papillary cystomas and epidermoid inclusion cysts. It is because of the extreme scarcity of reports of lymphangiomas or lymphangiectasis in this location that we feel justified in presenting a case of this sort, which has recently come under our notice.

REPORT OF CASE

History.—A white girl, aged 17, about five months in her first pregnancy, was seen in October, 1927. In the course of a routine examination an unusual prominence of the labia minora was noted. Close inspection showed a cystic growth in the left labium, and a simple thickening and general hypertrophy in the right. The patient denied a previous knowledge of the existence of this condition. Dr. Lyle B. Kingery saw the patient with us. From a general discussion we developed the impression that we were dealing with a benign cystic neoplasm, probably a lymphangioma, although from the clinical observations such a diagnosis was admittedly obscure. A biopsy and microscopic observations, however, proved this diagnosis to be correct. The past history was negative except for an attack of diphtheria as a child. The family history revealed that the mother and two sisters were living and well. We were unable to obtain a history of a similar condition in them. A general physical examination revealed nothing of significance aside from the condition which is the subject of discussion in this paper.

Gynecologic Examination.—The labia minora projected well beyond, and separated, the labia majora. They did not have the normal, pinkish, mucous membrane-like appearance of those normally found in nulliparous women; rather, their appearance more nearly approached that of the skin. There were no signs of inflammation or discharge.

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* Submitted for publication, Oct. 1, 1928.
* Read before the Oregon State Medical Society, Portland, Sept. 21, 1928.

1. Taussig, F. J.: Diseases of the Vulva, Gynecological and Obstetrical Monographs, New York, D. Appleton & Company, 1923, p. 136.

The lower three fourths of the left labium minus showed a tumor 5 by 2 cm. running lengthwise of the organ (figs. 1 and 2), and completely enclosed within its coverings. Translucent, soft, compressible, fluctuant, the tumor readily adjusted itself to conform to the topography of the tissues, and could be emptied or distended at will by forcing the fluid contents from one part to another. The right labium

Fig. 1.—Lymphangiectatic cyst of the left labium minus and hypertrophy of the right labium.

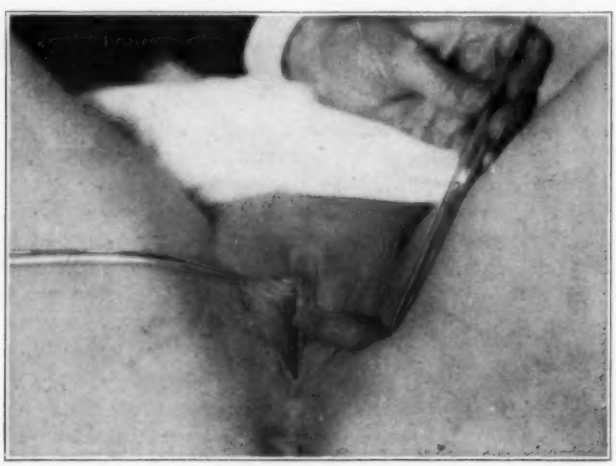

Fig. 2.—Showing the vulva; the labia is extended laterally with forceps.

minus appeared generally hypertrophic. Evidence of fluid contents could not be demonstrated. The tumor of the left labium was easily excised intact under local anesthesia. It was not thought justifiable to operate on the labium of the opposite side.

Macroscopic Examination.—An incision through the middle of the tumor revealed a spongelike mass immediately beneath the skin, which was composed of innumerable intercommunicating chambers. These differed in size from that of a

pinpoint to that of a split-pea, being separated by stroma varying from pink to white (fig. 3). The contents were clear, colorless and slightly viscous.

Microscopic Examination.—The epidermis (fig. 4) lay in irregular, wavy folds, corresponding to the usually described cockscomb appearance of the exterior. The

Fig. 3.—Transverse and vertical sections of the gross specimen of the tumor, showing polycystic cavities.

Fig. 4.—Section from the labium cyst. The corium shows dilated lymph spaces and cysts in the lower portion. Perivascular infiltration of small, round cells is present in the upper portion.

stratum corium was thicker in places than the entire epidermis. There was evidence of scaling. The stratum granulosum was well defined. The stratum mucosum, overlying the major portion of the cyst, showed distinct atrophy. The stratum germinativum was intact throughout, and was darkly pigmented.

Corium.—The papillae were, in general, peg-shaped or club-shaped, although in certain areas, they were nearly flattened out. The stroma was composed of spindle-shaped connective tissue cells which were relatively sparse in nuclei. Co-mingled with these were nonstriated muscle fibers. In certain areas near the epidermis, small clear spaces (fig. 5) separated the connective tissue cells. Deeper in the corium the spaces were larger; some had a cystlike appearance, others were tortuous channels, and contained occasional groups of red blood cells (figs. 4, 5 and 6). The cavities were mostly lined with elongated endothelial cells (figs. 6 and 7), which rested directly on the connective tissue stroma, and contained round or oval nuclei and an occasional nucleolus. In areas, the spaces were carpeted simply with young connective tissue cells. Some of the endothelial cells lay flat

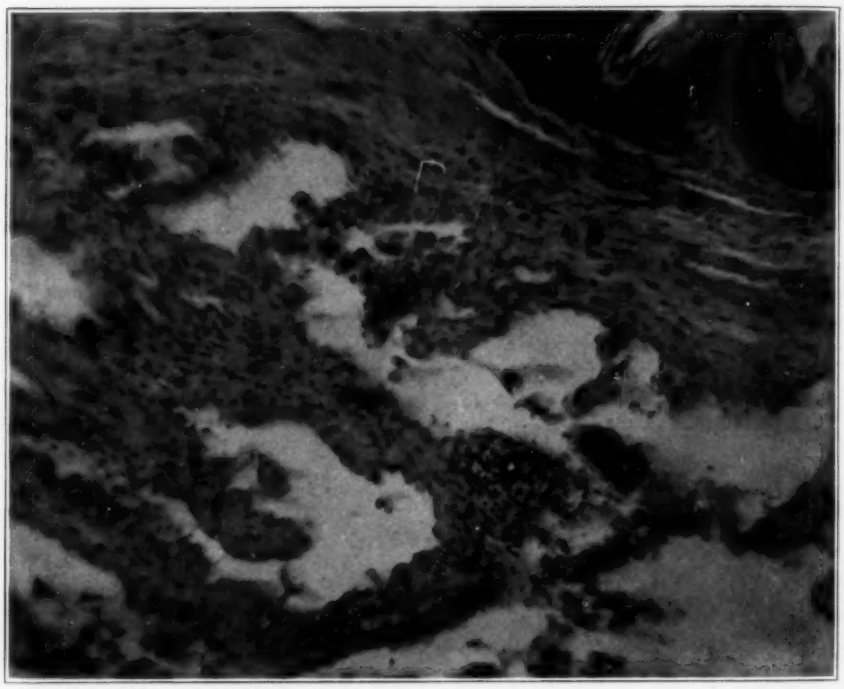

Fig. 5.—High power view of lymph channels and cysts lined with endothelial cells. Longitudinal and cross-section of small blood vessels in connective tissue with perivascular infiltration of small, round cells is shown.

against the stroma while others bulged into the lumen of the cavities. In places, small peninsulas of actively growing connective tissue, covered with endothelium, jutted out from the borders into the cavities. The connective tissue stroma separating the cysts was usually delicate, being from four to eight cell layers thick; occasionally, however, it was much wider, and contained lymph capillaries and small blood vessels (figs. 5 and 6). The corium, as a whole, showed a moderate amount of perivascular infiltration of small round cells. A few sebaceous glands were seen. The sections prepared with van Giesen stain did not show any increase in elastic tissue fibers. Unfortunately, by mistake and contrary to directions, the contents of the cyst were lost before chemical and microscopic studies could be made of them.

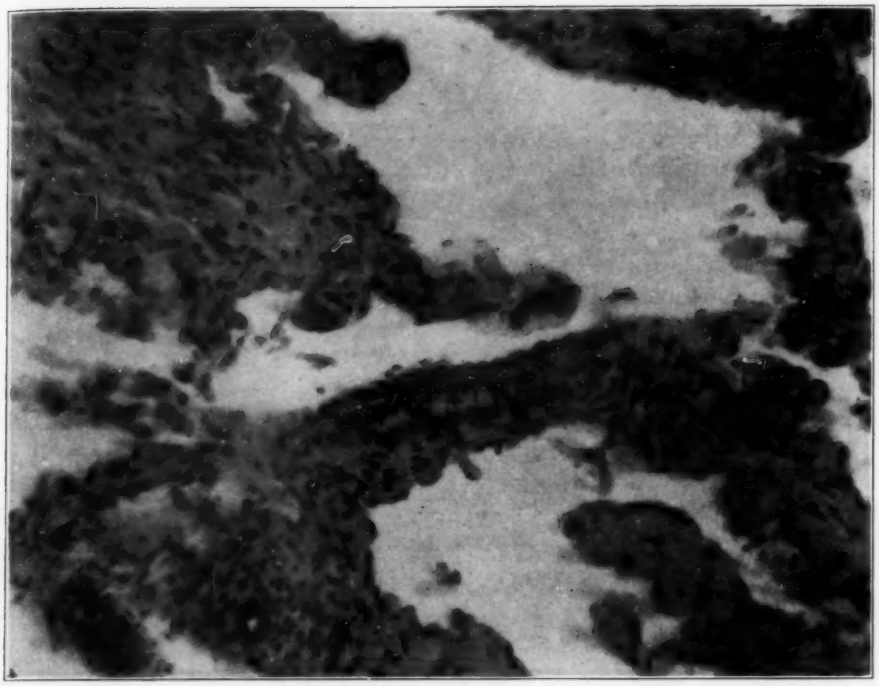

Fig. 6.—High power view of labium minus, showing lymphatic cysts lined with endothelial cells.

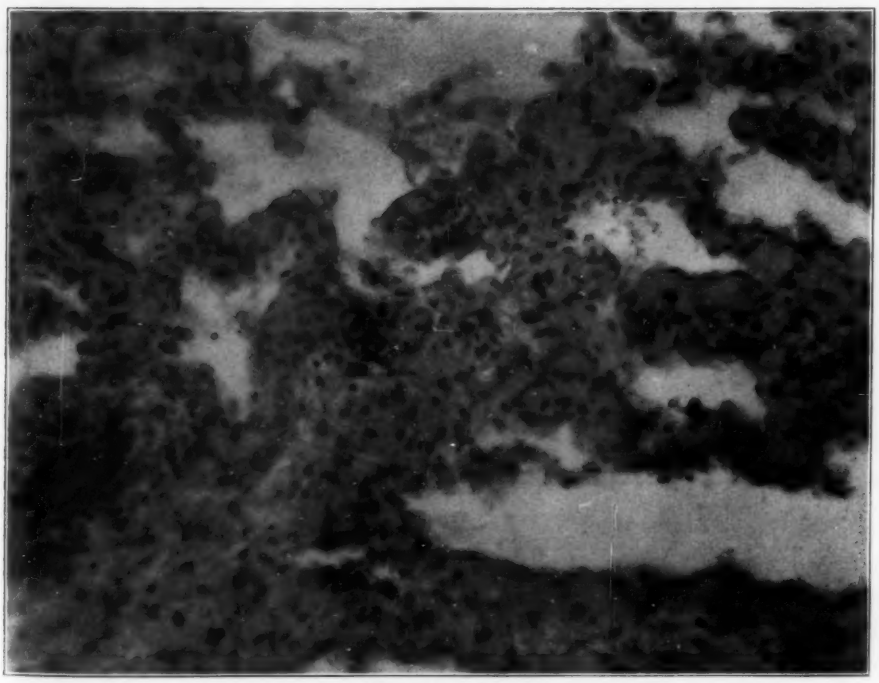

Fig. 7.—High power view of labium minus, showing lymphatic cysts and tortuous channels lined with endothelial cells.

CLASSIFICATION OF LYMPHANGIOMAS

Unna,[2] making no artificial distinction between lymphangiectasis and lymphangiomas, classified these growths on an anatomic basis in accordance as their main location affects the papillary body, the hypoderm or the large subcutaneous vessels. The tumors of the (1) papillary body are subdivided into: (*a*) lymphangioma superficiale simplex, which may be accompanied by wartlike epithelial growths, and (*b*) lymphangioma superficiale, which have a vesicular appearance and tend to rupture and to cause lymphorrhea. These cysts are frequently associated with deep-lying lymphangiomas. (2) Lymphangiomas of the hypoderm, which are from the beginning cavernous, are ultimately converted into multilocular cysts. This class is subdivided into: (*a*) lymphangioma tuberosum multiplex (Pospelow) and (*b*) lymphangioma subcutanum solitaire. The latter are soft, fluctuating tumors of varied size, usually found on the neck and upper part of the trunk, but occasionally on the genital organs. On sectioning, when they are fairly well circumscribed, a quantity of pure or bloody lymph exudes from them. The cyst then collapses and reveals a coarse-pored, spongy structure. Microscopically, the connective tissue in the young cavernous lymphatics is soft, cellular and fatty, and contains numerous blood vessels. In the older cavernous and cystoid cysts, the connective tissue is avascular and more fibrous. The cavities and lymph spaces are predominantly clothed by flat endothelium, but occasionally they are bordered simply by collagenous or fatty tissue. The cavernous spaces are empty or contain granular coagulated serum with occasional leukocytes and red blood cells. (3) Lymphangiomas of the subcutaneous vessels are mainly congenital, and embrace the dilatations of the vessels reaching from the cutis to the large intermuscular lymph trunks. These types of lymphangiomas may be localized or widespread, and are frequently found on the leg and seminal cords along with venous varix.

The tumor in our patient is clearly a type of lymphatic hypertrophy. Considering its morphology in relation to Unna's classification, it should be placed with the lymphangioma subcutanum solitaire. Did the large cyst of the left labium minus have as its beginning a hypertrophy similar to that seen in the less prominent right labium? We have no means of knowing. We have, however, at present under our care a young woman, who is pregnant, and in whom both labia minora have developed a hypertrophic condition clinically, almost identical with the right labium in this case. It will be interesting to observe the clinical course in relation to the advancing pregnancy; and in view of Brindeau's case which is cited in the review of the literature, to watch for the effects

2. Unna: The Histopathology of the Diseases of the Skin, translated by Normon Walker, New York, The Macmillan Company, 1896.

of delivery in such conditions. At delivery we will obtain a specimen of one of the labia for a microscopic examination, and will make a subsequent report.

REVIEW OF THE LITERATURE

Of the few cases of lymphangiomas reported in the literature in which the labia minora were seen to be involved, we have been able to obtain access to the following.

Epstein,[3] in 1892, reported the following case:

A woman, aged 40, syphilitic, first noticed the condition as "fine scattered pimples" in the hypogastric region at the age of 24. Developing gradually, the

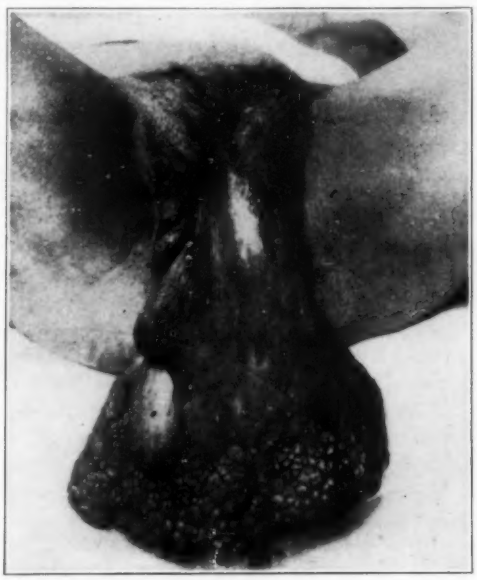

Fig. 8.—Patient discussed by Brindeau. Lymphangioma, the size of a "ham bone" with papules, attached to the labium minus.

condition finally included the hypogastric region, the right and left inguinal spaces, the pubic regions and the labia majora. Only the labia minora showed hypertrophy. Clinically, there was a central, red, raised, thick plaque surrounded by wartlike growths. The surface of the plaque was dotted with single or grouped vesicles. When these vesicles were opened, a clear, transparent, gelatinous fluid slowly exuded from them. Subjective symptoms were aching, burning and itching in the affected regions. The itching was intense when the vesicles were full, and was relieved when they were emptied.

Two points of interest are presented in this case: (1) a history of an occasional unexplained, spontaneous disappearance of the lesions; (2) their improvement under antisyphilitic therapy.

3. Epstein: A Case of Lymphangioma, J. Cutan. Dis. **10**:213, 1892.

In 1905, Brindeau [4] reported a case which is remarkable on account of the size of the tumor described.

A woman, aged 25, eight and a half months in her second pregnancy, was particularly noticed because of her difficulty in separating her thighs while walking and in bending forward. During the second month of the pregnancy, "while scratching" a "slight largeness on the genital organs" was first called to her attention. This increased in size, gradually, for three months, followed by a rapid increase to that of the "head of an adult." Examination revealed a tumor of the left labium minus, the size and form of a "ham bone" (fig. 8). On the portion covered by mucous membrane, and on the inferior surface were numerous papillae, varying in size from that of a "hazelnut to that of a plum." In the center of the papules and on its inferior surface was an ulcer the size of a "five franc piece," having a fetid discharge. Three days following the delivery of a normal child, the tumor, which had greatly decreased in volume, was excised. On section, "the tissue was gelatinous."

Although a description of its morphology was not given, the report stated that a microscopic section showed it to be a lymphangioma.

In 1905, Lehmann [5] presented a virgin, aged 22 years, with an elephantiasis vulvae and lymphorrhea. A detailed description of the growth was not given. The "affection at present involved both labia, perineum, mons veneris and the right thigh." There was a history of the removal of the "right labium" three years previously, and of a "lymphangiectatic tumor spreading diffusely into the adjacent tissues on the right side posteriorly." "A recurrence was again operated a year later, to reappear in its present form." There was no history of disease of the lymph gland apparatus. Results of pelvic examination were negative except for an atrophic uterus. The author thought that the case was one of constitutional anomaly. He referred to a somewhat similar case reported by Lesser, in 1891, before the Gynecologic Society of Leipzig, which differed from this one, however, in that it showed evidence of widespread scarring from a tuberculous involvement of the lymph glands, of many years' duration.

The latter case suggests the one reported by Stokes.[6]

In 1923, Stokes gave the history of a woman, aged 31, who presented elephantiasis of both lower extremities and lymphangiectasis of the vulva secondary to tuberculous obliteration of the inguinal glands and recurrent secondary streptococcic cellulitis. Both labia majora presented a picture suggestive of "condylomatous vegetations with dry, clean surface." On closer inspection, "translucent, lymphoid vesicles" were identified. Similar vesicles were seen grouped near the inguinal scars. The lesser labia were only slightly involved.

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4. Brindeau: Lymphangioma de la petite lèvre chez une femme enceinte, Bull. Soc. d'obst. et de gynéc. **8**:272, 1905.

5. Lehmann: Berichte aus gynakologische Gesellschaften und Krankenhausern, Zentralbl. f. Gynäk. **29**:750, 1905.

6. Stokes, J. H.: Acquired Lymphangioma of the Vulva, Secondary to Tuberculous Obliteration of the Inguinal Glands, Arch. Dermat. & Syph. **8**:498 (Oct.) 1923.

Stokes stressed two points as having particular interest: 1. Tuberculous infection of regional lymph glands may have the effect of a total surgical extirpation. 2. The successful application of radium in the treatment demands that it be applied locally to the glands as well as to the growth itself.

In 1923, Tobias [7] reported a case in a girl, aged 15, in whom the right labium minus, with the right half of the prepuce of the clitoris, showed a condylomatous hypertrophic mass covered with thickened edematous skin, and numerous transparent vesicles. The skin of the right perianal and perineal regions was verrucous and covered with a thin yellow discharge. The condition had been present since birth.

An interesting fact in the case was an associated nevus unius lateris involving the right half of the tongue and the vermilion border of the lips.

Unna [2] said that it is difficult to distinguish between lymphangioma and lymphangiectasis. Both have in common the venolymphatic stagnation and a universal endothelial growth, but in lymphangioma, the excess of cell material is evident either in the thickening of the wall or in an elongation of the vessel. Only when the border of the true lymph vessels reaches to the lymph spaces and invades their domain does an elongation of the vessel result and thus a lymphangioma. He also thought that the venous system was the proper source of every lymph stasis, that every lymphangiectasis requires a double resistance to the venous and to the lymphatic circulation, and that every lymphangioma requires, in addition, an abnormal power of proliferation of the endothelia and perithelia.

COMMENT

We have been able to locate in the literature the reports of only five cases of lymphatic cysts involving the labia minora. Of the five only in that of Brindeau was the growth limited to the labia minora as in our patient. We make no attempt to speculate on the etiology. In view of the prevalent confusion in the interpretation of the pathologic condition in such cases, we accept the suggestion of Dr. Frederick J. Taussig [1] and use the terms lymphangiectatic hypertrophy rather than lymphangioma or lymphangiectasis.

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7. Tobias, N.: Lymphangiectatic Hypertrophy of the Vulva, Occurring in a Nevus Unius Lateris, Arch. Dermat. & Syph. **8**:647 (Nov.) 1923.

GROSS AND MICROSCOPIC CHANGES IN THE SKIN PRODUCED BY X-RAYS AND BY LIPOID SOLVENTS *

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In a former communication [1] we stated that similar histologic changes in the tissue were noted after roentgen burns [2] and that lesions were produced in the skin of rats by repeated paintings of tar preparations over a long period of time.

By varying the time period of exposure and by transmitting the ray through an opening 1 cm. in diameter, the remainder of the rat being protected, we have produced various degrees of roentgen burns of the skin. Our observations were begun in February, 1927, and were continued to the time of preparation of this paper. We terminated the experiment because a large percentage of the animals in the series painted with coal tar preparation had died and, as we are especially interested in comparative data, the rest of the animals were killed and autopsies were made.

A large series was started so that one animal from each series could be killed every thirty to sixty days throughout the experiment, for study of progressive changes. Weights were taken every ten days to two weeks for the purpose of comparative data also. The area of skin exposed to the x-rays or painted with the tar preparation was removed, fixed in formaldehyde, dehydrated and stained with hematoxylin eosin. The whole procedure was uniform throughout.

TECHNIC

An area 2 cm. in diameter was denuded on the dorsal surface of the rat extending from the base of the skull posteriorly. A weak solution of sodium sulphide was used, the area being cleansed with alcohol, as soon as denudation was complete. In this way excoriations of the skin seldom followed. If excoriations occurred, the animal was not used in the experiment. The tar preparations

* Submitted for publication, Nov. 5, 1928.

* From the Departments of Research and Dermatology, The Barnard Free Skin and Cancer Hospital, and published as one of the series of studies, reports and observations from the dermatological departments of the Barnard Free Skin and Cancer Hospital and the School of Medicine, Washington University, St. Louis, Mo., U. S. A., service of Drs. M. F. Engman and W. H. Mook.

1. Jorstad, L. H., and Lane, C. W.: Comparative Studies of Histological Skin Changes Produced by X-Rays and by Lipoid Solvents, Proc. Soc. Exper. Biol. & Med. **24**:886, 1927.

2. We use the term "burns" for uniformity of description while "reaction" may have been a more desirable term in describing the lesions produced by the smaller dosages of x-rays, especially.

used consisted of the commercial tar ointment, U. S. P., full strength, (a mixture of pine tar and petrolatum) and coal tar solution, N. F. (an alcoholic solution of coal tar). In the beginning of the experiment these were applied every two days, but on account of the marked loss of weight resulting, the time interval was changed to twice weekly. The tar was applied with a cotton swab.

In the series in which roentgen burns were induced, the quantity of x-rays used varied from 5 to 50 milliampere minutes. The x-ray setup was 10 inch distance, 9 inch spark, 90 kilovolts; the period of exposure varied from one to ten minutes, the one minute exposure in this setup giving 5 milliampere minutes, and the ten minute exposure 50 milliampere minutes.

In addition, a number of the animals with definite roentgen burns were removed to separate cages and the area painted with the tar preparations already mentioned.

The animals in the series in which different dietaries were given were placed on these dietaries two weeks before the experimental manipulation was begun.

GROSS OBSERVATIONS

Tar Series.—The preparation of pine tar induced the most marked changes. After a period of two months the denuded area remained so, or only a sparse growth of hair resulted. At the end of from three to five months, a definite scaling appeared over the painted area, and the skin became dry with a tendency to crack or fissure. In one instance, a definite warty excrescence appeared, but it dropped off after a period of ten days. A definite thickening of the skin was noted. The same changes were noted grossly in the series painted with the coal tar solution, but to a less degree.

Some of the rats in this series were fed a dietary high in vitamin A, some a dietary low in vitamin A, and the majority a well balanced dietary. There were no marked differences in the gross appearance of the lesion induced in these animals on the different dietaries. Owing to the relatively short length of life of the animals on the dietary deficient in vitamin A, most of our observations were of necessity confined to the comparison of gross differences in the animals on the stock ration and in those on the high vitamin A dietary. The components of these dietaries have been given in previous studies issued from this laboratory.[3] The balanced dietary in this case is the stock ration. Animals on the high vitamin A dietary gain weight more rapidly and do not show ill effects from the painting with the lipoid solvent from the beginning of the experiment, as do the animals on a balanced stock ration. The latter animals, however, live for a longer period of time, and even though they show a less degree of initial gain in weight, they attain a

3. Burrows, M. T.; Jorstad, L. H., and Ernst, E. C.: The Chemical and Biological Changes Induced by X-Rays in Body Tissues, to appear in Radiology; Further Studies on the Effect of Graded Doses of X-Rays on Animals Fed on Various Dietaries, with a Note on the Effect of Dietary in the Treatment of Patients with X-Rays, Radiology **10**:209, 1928.

greater or the same weight after a few months on the dietary. As noted in previous studies, this is probably due to the greater ease of absorption of the lipoid solvent by the animals on the high vitamin A dietary,[4] the later loss of weight and eventual death probably being due to the marked deposition of fat in the liver of these animals. This occurs later in this series (tar painting) than in the series reported formerly, in which the lipoid solvent was introduced subcutaneously. It also occurred less consistently in this series.

X-Ray Series.—The time of appearance of the roentgen burn was taken as the first observation at which a definite, well outlined denuded area occurred at the site exposed. Gross lesions did not appear in the series of rats given 5 and 10 milliampere minutes of x-rays. They gained weight normally and lived the normal period of time. Partial denudation of hair occurred from sixty to ninety days after date of exposure in some of the rats given a dosage of 20 milliampere minutes of x-rays. These persisted as fairly well marked burns (partial denudation and a slight amount of, if any, scaling) throughout the period of the experiment. In the series of rats given 30 milliampere minutes, a well marked burn (complete depilation followed by marked dryness and scaliness of the skin) appeared from fifteen to twenty days after exposure to the x-rays. This persisted throughout the period of the experiment. With 40 milliampere minutes, the burn occurred fifteen days after exposure. During the first thirty days after appearance these were termed in our protocol as "very well marked" burns, on account of the complete denudation and earlier and marked scaling. After this period, however, they had practically the same gross characteristics as those in the rats in the series given 30 milliampere minutes. Well marked burns appeared in the animals given 50 milliampere minutes fifteen days after exposure, and these persisted as "well marked" or "very well marked" burns. The weight curves in the whole series did not present differences that could be attributed to the experimental manipulation. After a period of from thirty to forty-five days, the burns in the rats given 20 milliampere minutes of x-rays showed evidences of healing in that the lesion became less distinct. The burns in the rats given 30, 40 and 50 milliampere minutes persisted throughout. The degree of scaling and fissuring in the animals given 30 milliampere minutes was less than in the two higher series, gross changes in the rats given 40 and 50 milliampere minutes being similar. The scaling, fissur-

4. Jorstad, L. H., and Johnston, C. G.: Local and Systemic Changes Induced by Lipoid Solvents in Animals Fed on Diets Varying in Vitamin Content, Am. J. Path. **3**:489, 1927; Reaction Produced by Lipoid Solvents in Animals Fed Dietaries Deficient and High in Vitamin A, Proc. Soc. Exper. Biol. & Med. **24**: 86, 1926. Jorstad, L. H.: Studies on Fatty Infiltration of the Liver Induced by Lipoid Solvents, ibid. **24**:723, 1927.

ing, attempts at healing and scarring noted grossly are similar to those described for roentgen burns in man. The animals in the x-ray series were fed a well balanced stock dietary.

Appreciable differences in the gross appearances of the burn induced were not noted in the animals on the rich vitamin A dietary. For a period of sixty days until the burn became well marked, these animals gained weight more rapidly than did those given a well balanced dietary. At this time they attained a level comparable to those on the stock ration, but after the tenth month they lost weight rapidly, and 50 per cent of the series died at the eleventh month.

The animals on the low vitamin A ration gave some interesting data in that fairly well marked burns appeared with the 20 milliampere exposure. The animals given 5 milliampere minutes did not develop burns, but the striking thing in repeated series was the gradual gain or no appreciable loss of weight and no evidence of xerophthalmia until the fifth month. After one 10 milliampere minute exposure the signs of deficiency did not occur until the sixth month, and with 20 milliampere minutes they appeared at the eighth month. The animals given 30, 40 and 50 milliampere minutes lived from forty to sixty days after exposure and developed well marked burns from fifteen to thirty days after the exposure. At the time of appearance of xerophthalmia the animals in the series given 5, 10 and 20 milliampere minutes were placed on a dietary containing a slight amount of vitamin A; this caused a small increase in their rate of growth and a definite increase in their activity, but the animals given 5 milliampere minutes developed severe symptoms of vitamin A deficiency and died. The rationale in this procedure was to carry these rats along for a time on a ration just high enough in vitamin A to prevent a severe deficiency and to compare the resultant histologic changes in the exposed area with the lesions obtained in the rats on the other rations. Grossly, the burns presented the same characteristics as noted for other series. Even though burns appeared in the animals on the deficient vitamin A ration in the series given 20 milliampere minutes, there were no striking differences in gross appearances of the burns in this series as compared to the other series.

Combined Treatment Series.—In this series we painted well marked roentgen burns with the tar preparations twice weekly. We noted an increased scaling and fissuring as compared to the unpainted roentgen burns. There was definite scarring and flat verrucous formation in all of them. These did not persist, but dropped off after a few days. They gave the characteristics grossly of accumulations of keratin intermixed with the tar preparation.

HISTOLOGIC DATA

Tar Series.—Within from thirty to sixty days there was a definite keratosis of the area of skin to which the tar preparation had been

applied. For a period of ninety days this was rather superficial. At this time or later many of the sections showed this keratosis as involving the hair follicles, the keratohyalin being formed in the lumen. Hyperplasia of the epithelial cells lying underneath the keratotic area appeared at this time or earlier. It is in the most marked keratotic areas that hyperplasia was greatest in degree. From this period until the ninth month the sections presented only slight differences, the keratosis and hyperplasia remaining at practically the same degree. At this time, however, most of the sections showed a definite precancerous lesion or early cancer of the squamous cell type. The epithelium was greatly thickened, the upper part was made up of keratohyalin in plaque, fibrillar and occasionally whorl (pearl) formation. The thickening was not due to edema as is usually seen in the sections from thirty to sixty days after the painting with tar had been started. There were definite pearls in this epidermis scattered in areas throughout the treated skin. In these areas especially there were cells with deeply staining nuclei, the layer being from fifteen to twenty cells in thickness. Some sections showed a definite heterotopia of the lower stratum or surrounding pearls in the middle layer. The cells involved were not strictly of the basal cell type, the whole lesion giving the appearance of the squamous or prickle cell type rather than the basal cell type of carcinoma. The corium appeared normal until these definite precancerous lesions were formed, at which time there was a slight amount of round cell infiltration and a definite decrease in the depth of eosin staining (fig. 1).

X-Ray Series.—Permanent histologic changes were noted in the burns only in the animals given 20, 30, 40 and 50 milliampere minutes; thus description will be limited to these series. The striking feature of these lesions is destruction. In the burn in the animals given 30 milliampere minutes the epithelium is intact within thirty days, but is markedly thinned. In from sixty to ninety days and up to eight months this degree of burn showed a definite hyperkeratosis of mild degree, a consequent thinning of the epithelium and a marked hyalinization of the corium which involved some of the glandular structures therein. Scattered throughout the extent of the burn there were areas of thickened hyperplastic epithelium, but this hyperplasia was not so extensive as in the series already described; neither was it so marked as that of some of the hair follicles in this same area. At the fourth to eighth month period and later some of these follicles showed a marked hyperplasia, but none developed into folliculo-epithelioma; yet they had the characteristics of a marked precancerous condition.

In the animals given 40 and 50 milliampere minutes the hyalinization was more marked; the epithelium remained as a thin layer of keratotic cells or was entirely flaked off in the form of plaques. The hyalinization of the corium was well marked, the whole layer at the

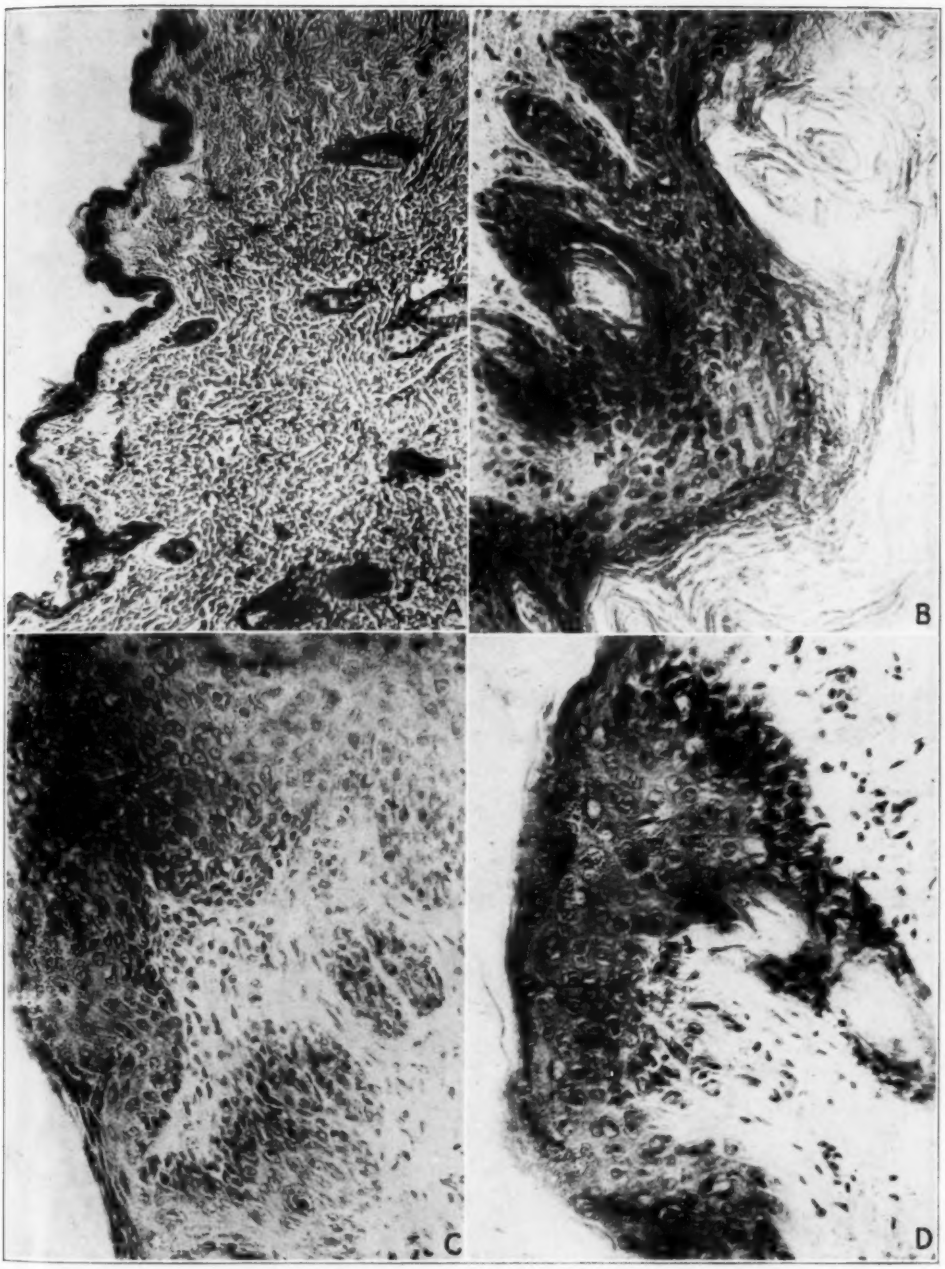

Fig. 1.—Moderately high power photomicrographs of sections of skin of adult rats; *A*, section from skin of adult rat to serve as control; *B*, section from area of skin of adult rat painted with tar ointment, U. S. P., twice a week over a period of thirty days; *C*, section from area of skin of adult rat painted with tar ointment, U. S. P., twice a week over a period of sixty days and *D*, section from an area of skin of adult rat painted with tar ointment, U. S. P., twice a week over a period of ninety days.

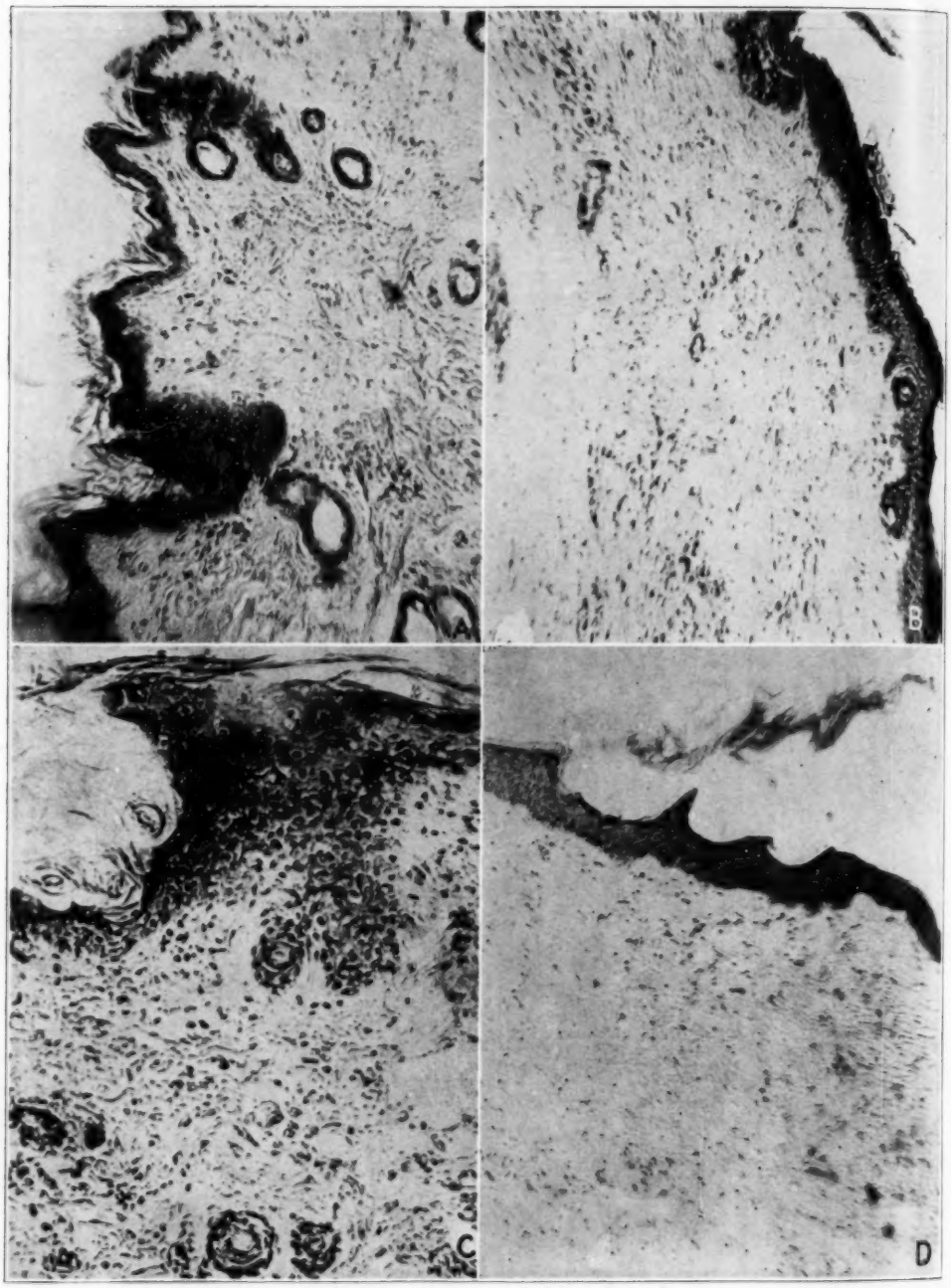

Fig. 2.—*A*, section from area of skin of adult rat fifteen months after 30 milliampere minutes of x-rays; *B*, section from area of skin of adult rat fifteen months after 30 milliampere minutes of x-rays, area having been painted with tar ointment, U. S. P., twice a week after the roentgen burn appeared; C, section from area of skin of adult rat six months after 40 milliampere minutes of x-rays, area having been painted with tar ointment, U. S. P., twice a week after the roentgen burn appeared and *D*, section from area of skin of adult rat twelve months after 30 milliampere minutes of x-rays, area having been painted with tar ointment, U. S. P., twice a week after the roentgen burn appeared.

sixty to ninety day period or later being thin, owing to the shrunken state of the fibrous tissue as compared to the normal, as well as the destruction of the blood vessels. The striking feature was the poorly stained shrunken corium and the sparsity of glandular tissue, as most of these structures had been destroyed. This hyalinization extended down to and in some cases involved the underlying mascularis, especially in the animals given 50 milliampere minutes. At the edges of these burns the bordering epithelium presented an edge which showed definite signs of attempted healing, and in some cases it extended down into the hyalinized tissue of the burn proper. These lips showed moderate amounts of hyperplasia. Occasionally, moderate amounts of hyperplasia were noted in the hair follicles situated in the deeper portions of the burn. This was true in the animals given 40 milliampere minutes. Thus the histologic picture during the first six to eight months was that of a destructive process with those higher dosages as compared to the combined destructive and hyperplastic process in the animals given 30 milliampere minutes.

At the fifteenth month the epithelium overlying the burn from an exposure of 40 milliampere minutes was not completely destroyed, but the hair follicles were practically absent. At this time the epithelium in this series as well as in the series in which the animals were given 30 milliampere minutes was markedly hyperplastic. In certain areas it was from fifteen to twenty cell layers in thickness. This change was more marked in the animals given 40 milliampere minutes. The areas presented the same characteristics as the precancerous lesions described in the animals painted with tar, so far as the epithelium was concerned. The lesions in these two series can be differentiated, however, in that the lesion in the animals painted with tar presented a marked hyperkeratosis with a slight amount of hyalinization of, or a normal, corium. The roentgen lesion presented a marked hyalinization of the corium and a slight amount of hyperkeratosis.

In the animals given 50 milliampere minutes the zone of epithelium and hair follicles surrounding the burn showed marked hyperplasia at the fifteen month period. At this time the roentgen burns presented practically the same amount of precancerous hyperplasia as was evident in the animals painted with tar at the fourth to the sixth month (fig. 2 *A*).

Combined Series.—The keratosis was less marked in this series than in the series in which the animals were painted with the tar preparation only. The epithelium was thin, except in scattered areas, in which there were a definite thickening in the form of a definite hyperplasia of epithelial cells, in some places ten cell layers deep. The keratosis was most marked over those areas. Only animals with burns produced by an exposure of 30 and 40 milliampere minutes were used in this series. The most marked hyperplasia was at the margins of the lesions, and in

these areas the hyperplasia of hair follicles in the corium was especially noted. In the burn from an exposure of 30 milliampere minutes, the painting having been begun as soon as the burn appeared, the lesion eight months afterward was that of a thinned epithelium and corium. This involved the whole area down to the muscularis. The lesion was a hyalinized band of tissue one-third narrower than the normal tissue surrounding. As compared to the burns produced by the same technic except for the painting with tar the condition in this series showed a more marked destructive process, the hyperplasia being limited to fewer areas and especialy to the edges of the lesion. There was no marked difference in the amount of hyperplasia of the hair follicles in the animals in this series and in those with roentgen burns not painted with the tar preparation (fig. 2 *B*).

RÉSUMÉ OF HISTOLOGIC DATA

In the white rat painting the skin with tar ointment, U. S. P., induced a marked hyperkeratosis within thirty days. At ninety days, or earlier, a definite hyperplasia of the epithelium was induced, and at from four to six months the marked heterotopia and extension of the pegs as well as pearl formation throughout the whole layer of skin completed the picture of an active precancerous lesion. The nature of the tar preparation and the infrequency of application prevented the appearance of ulceration as well as a high death rate of animals in the early part of the experiment.

The most active lesions in the animals with roentgen burns occurred in those induced by 30 and 40 milliampere minutes, the specimens being taken fourteen months after exposure to the x-rays. In these specimens there was marked hyperplasia and heterotopia of the epithelial layer with an extension downward throughout the hair follicles and a spreading of cells outward from these deeper lying structures. This lesion did not present the marked keratosis that was produced in those rats in which the skin was painted with the tar preparations only. The corium was markedly hyalinized.

The most active lesion in the animals painted with the tar preparation only occurred 120 days after the beginning of the painting, the application being made twice a week over the period of time. The earliest appearance of marked hyperplasia and hyperkeratosis was noted at forty-five days. These lesions were different from those in the other series. There was a greater tendency to pearl formation during the later periods; the animals painted with tar presented a flattened area of hyperplasia, the lesion in the animals with a roentgen burn being not so flattened and having a definite hyperplastic and precancerous involvement of the hair follicle as well as the superimposed epithelial layer.

COMMENTS

In a review of the more recent literature dealing with the experimental production of cancer, the factor emphasized is that "irritation" as a specific cause of the induction of a malignant condition has become less important. No specific carcinogenic substance or body has been found in any of the substances which produce a malignant growth in nonresistant animals. Pure and simple irritation may not produce cancer in these susceptible animals, as has been recently emphasized by Rosentirn.[5] In using various preparations of iodine, he found that alcoholic and aqueous solutions painted for eighteen months on the skin of 200 white mice known to be susceptible to cancer produced a local infiltration only, with lymphocytes and fibroblastic elements predominating. Fibrosis of the deeper structure without evidence of hyperkeratosis was the final observation in the experiment.

Numerous investigators have produced carcinoma in mice by painting them with crude coal tar or fractions thereof. The malignant transformation has been proved histologically and by transplantation. In a review by Louis Herly in a recent publication, he stated that precancerous warts appear between the eighty-fifth and the two hundredth day in mice, the great majority appearing at the one hundred and twentieth day, as a result of painting with coal tar.[6] Besides the production of tar cancer on the back of the mouse and on the ear of the rabbit, reports have been made of the experimental production of cancer in the rabbit's breast, and on the wall of the rabbit's stomach and lung by means of inhalation and injection of coal tar. Russel[7] reported a metastasizing tumor (histologically a sarcoma) as the result of injection of coal tar into the flank of a white rat. This occurred once in a series of forty rats.

In the same communication, Herly cites Bullock's determined effort to produce a malignant condition in the white rat. In a series of 185 rats, painting with coal tar on the back produced a few nodules of the skin in only one rat of the series, and this occurred sixteen and one-half months after the beginning of the experiment. The remainder of the animals did not show pachydermia, hyperkeratosis or warts, but only a temporary alopecia.

Herly reported that by using gaswork tar, diluted to 50 per cent with glycerin, to which 1 per cent arsenious acid was added, he produced alopecia, pachydermia, hyperkeratosis and a few papillomatous

5. Rosenstirn, J.: Iodine Irritation Does Not Produce Cancer, J. Cancer Research **10**:61, 1926.

6. Herly, Louis: Experimental Production of Tumor in a White Rat, J. Cancer Research **10**:102, 1926.

7. Russel, B. R. G.: An Experimental Production of Tar Sarcoma in Mice and Rats, J. Path. & Bact. **25**:409, 1922.

growths over the surface of skin in a series of white rats painted three times a week over a period of 226 days. Only sixteen rats survived after a further interval of five months of suspended painting. With resumption of painting at this time a definite skin horn developed at 511 days in one rat; microscopically, this had the features of a tar cancer in mice. The further results of this experiment have not been reported by the author. The mortality rate as cited by Herly is the usual one noted in the experimental production of tumors with coal tar or allied substances. The death rate is the result of a toxic condition due, no doubt, to the absorption of the tar. Passey and Braine [8] emphasized this factor in their studies of the induction of malignant lesions in mice by painting the skin three times a week with household soot. By fractionation these authors found the ether-soluble bases to be most active in the production of epithelioma. In the same journal, Passey and Woodhouse [9] reported that they did not find marked differences grossly and microscopically as to the appearance and character of the tumors formed by this technic in two groups of mice, one fed a dietary rich, and one deficient, in vitamin A. On account of the relatively short life of the animals on a deficient vitamin A dietary, however, this procedure is not a good one for this type of experiment.

Another communication interesting in this regard is that of Fischer-Wasels [10] from Munich, in that he observed that scarlet red dissolved in liquid petrolatum repeatedly injected into the mammae of female mice produced adenocarcinoma with metastasis from twelve to eighteen months after injection.

A number of general conditions and changes and their relationship to the local carcinogenic transformation must be considered. Davidson [11] observed acute changes in the liver similar to those in acute yellow atrophy in chronic changes resembling the typical atrophic type and regenerative changes with adenomatous peculiarities in a series of rabbits free from coccidiosis, pine tar being applied to the ears or injected subcutaneously dissolved in ether. One of us (L. J.) noticed similar degrees of hepatic necrosis in rats painted with or receiving subcutaneous injections of coal tar and allied substances.[12] No doubt,

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8. Passey, R. D., and Braine, J. C.: Experimental Soot Cancer, J. Path. & Bact. **28**:133, 1925.

9. Passey, R. D., and Woodhouse, J. L.: The Influence of the Fat Soluble Accessory Food Factor on the Initiation of Soot Cancer in Mice, J. Path. & Bact. **28**:145, 1925.

10. Fischer-Wasels, B.: Experimental Production of Mammary Carcinoma, München. med. Wchnschr. **75**:73, 1928.

11. Davidson, J.: On Liver Necrosis and Cirrhosis Produced Experimentally by Coal Tar, J. Path. & Bact. **28**:621, 1925.

12. Jorstad, L. H.: The Behaviour of Coal Tar in Adult and Embryonic Tissue, J. Cancer Research **9**:232, 1925; The Relation of Vitamins to the Reaction Induced by Coal Tar in the Tissues of Animals, J. Exper. Med. **42**:221, 1925.

other workers have observed the same condition, but they have not been so fortunate as to observe it consistently in a definite series as has Davidson.

A number have reported the presence of coal tar and allied substances in other parts of the body than that into which it was injected or to which it was applied. One of us (L. J.) has observed coal tar in the superficial vessels a considerable distance away from the site of inoculation,[13] and has observed it in the lungs of white rats into which the tar had been injected subcutaneously [12] (thus ruling out definitely inhalation of the substance, and Johnston and one of us (L. J.)[4] observed the presence of a number of lipoid solvents in the regional lymph nodes and occasionally in distant ones following subcutaneous introduction of one or a mixture of them. In addition, it was noted that a high vitamin A dietary for a considerable period of time prior to the subcutaneous injection of one or a mixture of lipoid solvents, induces a diffuse fatty infiltration of the liver in these animals. The time of appearance of the fatty infiltration varies consistently with the nature of the lipoid solvents used. The animals on stock rations show a slight amount and those on a deficient vitamin A ration do not show any infiltration of the liver.

Thus, in reviewing the literature, especially in the light of observations made in this laboratory, the local and systemic action of coal tar and allied substances may be referred to their lipoid solvent properties. This was especially emphasized by the marked local differences in tissue reaction obtained when these substances (coal tar, paraffin oil, olive oil and neat's foot oil) were injected into the subcutaneous tissue of animals on dietaries rich and poor in vitamin A. Each substance breaks up more readily when a high rather than a low vitamin A dietary is used, but the less viscid oils break up more readily than the highly viscid coal tar. Again, by extracting much of the lipoid from the coal tar with ether before injecting it into the tissue, one obtains a marked local tissue reaction even in rats on a high vitamin A dietary. In this case the solvent has been altered so that its lipoid solvent ability has been increased. In the former case, the body into which the lipoid solvent has been introduced was depleted of a portion at least of its lipoids. With the extraction of these lipoids from the tissues by the lipoid solvent, hyalinization is induced. The theoretical considerations have been discussed in the previous communications mentioned. From these observations it is indicated that in addition to considering the particular animal in which one is attempting to induce a malignant lesion, due consideration must be given to the nature of the substance used to induce the condition. The data in this experiment have substantiated

13. Jorstad, L. H.: Unpublished notes.

our former contention that a certain group of substances, of which coal tar is one, induce a malignant condition in that they absorb the lipoids or a part of them from the tissue with which they come in contact. This one, or group of lipoids in the tissue, has been called the ergusia. The presence of this substance and its relation to the function of the tissues of which it is a part have been discussed by Burrows [14] and Burrows et al.[15] Jorstad and Johnston [4] and Jorstad and Glenn [16] did not note striking differences in the action of these lipoid solvents, whether they were of animal, vegetable or mineral origin, when they were injected into the tissue. All of them are absorbed slowly, even to gross observation, and it is questionable whether minute particles are not to be found in the tissues at indefinite periods of time following the injection. Some authors cite the absence of a definite tumor mass as the evidence of complete absorption, but this is erroneous, as evidenced by the observations following injections into the muscle tissue.[16] Dutcher and his associates [17] substantiated the observations of Burrows and Farr [18] that mineral oil fed to laboratory rats acts as a solvent for vitamin A. Studies in this laboratory have indicated that vitamin A supplies the lipoid-ergusia to the system. The amount of depletion of this substance plays an important rôle in the production of a malignant condition in a certain group of cases. With the removal of the ergusia from a cellular area, the archusia becomes increased in proportion over that compatible with normal growth, and independent growth of such an area results. The index of removal of the ergusia is that of presence or absence of hyalinization. As Burrows stated, a completely hyalinized mass is one from which most or all of the ergusia has been removed, the protoplasm precipitating as a result of the removal.

As stated previously,[1] the histologic changes in the skin produced by x-rays and by lipoid solvents are the same, the variance being a matter of degree, depending on the strength of the agent used. By painting the skin at repeated intervals with the diluted lipoid solvent (tar ointment, U.S.P.), we obtained hyperkeratosis, alopecia and warty growths followed by precancerous changes in the skin. The extent and degree of

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14. Burrows, M. T.: Energy Production and Transformation in Protoplasm as Seen Through a Study of the Mechanism of Migration and Growth of Body Cells, Am. J. Anat. **37**:289, 1926; The Nature of Atrophy and Hyalinization of Cells and Tissues, J. Cancer Research **11**:72, 1927.

15. Burrows, M. T., and Jorstad, L. H.: On the Source of Vitamin A in Nature, Am. J. Physiol. **77**:38, 1926.

16. Jorstad, L. H., and Glenn, F. H.: The Action of Oils in Muscle Tissue, J. A. M. A. **90**:26 (Jan. 7) 1928.

17. Dutcher, R. A.; Ely, J. O., and Honeywell, H. E.: Vitamin Studies, Proc. Soc. Exper. Biol. & Med. **24**:953, 1927.

18. Burrows, M. T., and Farr, W. K.: The Action of Mineral Oil Per Os on the Organism, Proc. Soc. Exper. Biol. & Med. **24**:719, 1927.

these changes depended on the frequency and period of application. A less frequent application over a short period of time causes a superficial keratosis, and a more frequent application causes a keratosis involving the whole layer. In the first series we obtained precancerous lesions, the cell layers underlying the keratotic layer undergoing hyperplasia and heterotopia. The most active lesions are found when this process has taken place in an area of skin overlying a hair follicle. These substances act then only to induce the cancer. Coal tar injected subcutaneously into the white rat causes extensive hyaline changes in connective tissue.[19] In cellular tissue of experimental embryomas it causes, in addition to the hyalinization, areas of cellular hyperplasia and in some cases epitheliomas or marked connective tissue proliferation, depending on which tissue is predominant in the area surrounding the droplets of coal tar. Our studies indicate that the action of x-rays is the same when small doses are given to the skin, in that we obtain a definite hyperplasia of the more cellular epidermis or glandular structure of the skin and hyaline changes of the connective tissue. Larger doses cause necrosis of the epidermis and glandular structure as well, with a more extensive degeneration of the connective tissue fibrils, the blood vessels and lymphatics of the dermis. The epithelium and glandular structures in the derm on the edges of such a lesion show the hyperplasia, as seen in the less extensive burns.

CONCLUSIONS

Active precancerous lesions histologically have been produced in the skin of the white rat by repeated painting with a diluted tar preparation. The same type of lesion is produced by a single exposure of unfiltered x-rays, or by combining the two procedures. In observing the histologic changes produced by these procedures at different intervals throughout the period of experiment, further evidence was gained that coal tar, allied substances such as mazola oil, paraffin oil and neat's foot oil, and x-rays act similarly in inducing a malignant condition. They act as lipoid solvents.[20]

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19. Jorstad, L. H.: Some Biological Factors in the Study of Cancer, with Special Reference to Their Relationship to Precancerous Lesions of the Skin, Arch. Dermat. & Syph. **18**:351 (Sept.) 1928.

20. Dr. Fred A. Hecker, of Ottumwa, Iowa, presented a paper before the American Association of Experimental Pathology, last April, in which he described the histologic changes obtained in the skin of rats which had been exposed to a number of dosages of x-rays. I had the pleasure recently of seeing the microscopic slides from these experiments, and the changes taking place are similar to those which we observed. The relationship of hyalinization to hyperplasia is as striking in his sections as in ours. In further studies he has shown that the injection of calcium chloride into this area further increases the hyperplastic process and tends to produce metastasis. His further studies along this line will be interesting.

Editorial

SHORT MEDICAL PAPERS

In *The Journal of the American Medical Association* of April 13, the second paper among the original contributions consisted of a quarter of a page—to be exact, twenty-eight lines of one column. It was a valuable paper. It covered the incidence of syphilis among prisoners at the California state prison at San Quentin, and gave the results of the examination of 10,000 patients for this disease.

Attention is called to it as an illustration of the fact that papers that cover what the author has to say and then stop may be important communications, no matter how short. Most papers are written to consider one definite point or, perhaps, one point and its collateral facts, and such papers are apt to be the most valuable. Certainly they are the most likely to be read and to be found, if the titles are good, when one is looking over the literature that the papers cover. Papers do not have to be short to be good, but it is a good index of the quality of a paper that it covers the subject considered and then ends. Of course, the sort of paper one should write depends on one's audience. It is sometimes desirable to include the history of the subject, the symptomatology, etiology, pathology, diagnosis, prognosis and treatment. But this sort of material in a paper purporting to present any original idea is usually just padding. Not only does it consume valuable space and waste the reader's time, but it obscures the point—if there is a point—that the writer is trying to emphasize. Einstein's latest exposition of his theory, on which he is said to have been working for years, was published in six or seven typewritten pages. It is a safe guess that in this paper he did not undertake to summarize all the information bearing on the subject from Newton to Michelson.

News and Comment

DEATHS

Dr. Domenico Majocchi, formerly professor of dermatology in the University of Bologna, and known for his description of purpura annularis telangiectodes, died recently in his eightieth year.

Dr. Domenico Barduzzi, rector and professor of dermatology in the University of Sienna, recently passed away.

Obituaries

F. A. BALZER, M.D.

1849–1929

In the recent death of Dr. Balzer, French dermatology loses one of its better known exponents. Born in Rennes, Brittany, of Swiss extraction, Balzer received a portion of his medical training there and finished at Paris, where he became an intern in 1874. At first he devoted much time to histology, and became chief of the histologic laboratory of the Faculty at Hospital Saint Louis. In 1878, he presented an inaugural thesis dealing with bronchopneumonia, which was instigated by Charcot. After becoming physician to the hospitals of Paris, Balzer was chief of service successively at Broca, Ricord and Saint Louis. He was one of the earlier pupils of Ernest Besnier.

Among his contributions may be mentioned studies on gonorrhea, chancroid, syphilitic bronchopneumonia, pigmentary syphilid, the fever of secondary syphilis, syphilis of the kidney and paroxysmal hemoglobinuria. He was much interested in the treatment for syphilis and made extensive researches on the use of mercurial oil, mild mercurous chloride and benzoate of mercury. He is credited with first calling attention to bismuth as an antisyphilitic agent (1889). With Griffon, he showed the importance of the streptococcus in impetigo and in ecthyma. Balzer also wrote an excellent textbook on syphilis and the venereal diseases.

He became a member of the Academy of Medicine in 1908; later, he was its vice president and would have been president but for his last illness. Among his other honors were the presidency of the French Society of Dermatology and Syphilography and Officer of the Legion of Honor. Those who frequented Saint Louis before the World War remember him as a most kindly man whose clinics were popular.

A. SCHUYLER CLARK, M.D.

1874–1929

Dr. Clark died suddenly from an attack of angina pectoris on March 22, 1929. He was born at New Brunswick, N. J., on July 26, 1874, and was the son of John S. Clark and Sarah Voorhees. He attended the Rutgers Preparatory School and Rutgers University, which conferred on him the degrees of B. S. in 1895 and M.S. in 1898. His medical education was obtained at the College of Physicians and Surgeons, Columbia University, from which he graduated in 1899. After obtaining his medical degree, he served as intern for eighteen months at Roosevelt Hospital, New York. He entered the field of dermatology in 1903, and was associated with the late Dr. L. Duncan Bulkley, both in his office and in his service at the New York Skin and Cancer Hospital. His success in dermatology was marked from the beginning, and at the time of his death he was attending physician to the New York Skin and Cancer Hospital, consulting dermatologist to Roosevelt, Ruptured and Crippled, Lincoln, Beekman Street, St. Peters', New Brunswick and All Souls hospitals. He was a member of the American Medical Association, the New York Academy of Medicine, the New York Dermatological, New Jersey State and New York state and county societies, and he was an honorary member of the Brooklyn Dermatological Society. His war record was Lieutenant, Army Medical Corps, 1917; Captain, April, 1917; Major, December, 1917; Lieutenant Colonel, Reserve Corps, June, 1919. He was a member of the Delta Phi Fraternity, the Omega Fraternity, the University, Riding, Fairfield County Hunt, Country Club of Fairfield, Pequot Yacht, Yeamans Hall, Deepdale and Leash clubs. In his chosen field of skin diseases, he wrote numerous articles and did pioneer work on radium, the x-rays and arsphenamine.

He was married in 1911 to Carrie Leverich Riker, who, with one son, survives him.

In the death of Dr. Clark dermatology has suffered a great loss.

Abstracts from Current Literature

THROMBO-ANGIITIS OBLITERANS. LEO BUERGER, Arch. Path. **7**:381 (March) 1929.

Typical lesions of thrombo-angiitis obliterans were reproduced in healthy veins by means of perivascular implantation of clot from cases of acute thrombo-angiitis obliterans. The experiments were performed on eight persons. In two, infection of the wound resulted; in two others, thrombosis occurred without any evidence of inflammation, and in the other four, typical lesions developed. The technic is described in detail.

THE DEADLY UPPER LIP INFECTION. H. J. JURGENS, Illinois M. J. **55**:273 (April) 1929.

On this important subject, the author finds that only about twenty-five papers have found their way into the European and American literature. He stresses the importance of avoiding surgical intervention in these cases, and cites two disastrous experiences in his early years of practice. Infections on the upper lip are different from similar infections elsewhere because of the anatomic make-up of the parts, the facility for rapid multiplication of organisms and because the location lends itself readily to trauma. Treatment is essentially expectant. A "let alone policy" must be adhered to. If in spite of this, the route of infection should take the course of the angular vein, or the anterior facial vein, or if it travels by contiguity to the soft structures of the neck, surgical intervention is sometimes of help in checking the progress.

SODOKU TREATMENT IN PARESIS. ALEX. S. HERSHFIELD, O. A. KIBLER, SELMA COLBY, M. T. KOENIG, O. W. SCHMID and ANNY MAREA SANDERS, J. A. M. A. **92**:772 (March 9) 1929.

Seventy-two patients with paresis were inoculated with the organism of rat bite fever. Blood from an infected guinea-pig was injected into the patients' thighs. About one half of the patients showed some physical improvement; 20 per cent showed mental improvement. In 60 per cent of the patients no mental changes were noted, and about 10 per cent became worse mentally. Neurologic improvement could not be demonstrated; the Wassermann test of the spinal fluid and the Lange tests did not show much change though a few negative reactions were noted. Apparently there was no relationship between the height of the fever and the degree of improvement.

A CASE OF DERMAL MYIASIS CAUSED BY PHORMIA REGINA MEIG. M. A. STEWART, J. A. M. A. **92**:798 (March 9) 1928.

A case is described of pustular dermatitis of the scalp with ulceration due to the black blow fly. The characteristics of the caustive agent, *Phormia regina,* are described in full.

DERMATITIS IN THE RUBBER INDUSTRY DUE TO A HYPERSENSITIVENESS TO HEXAMETHYLENAMINE. WALTER S. BURRAGE, J. A. M. A. **92**:799 (March 9) 1929.

The author points out that cases previously reported stressed the chemistry of the mechanism, and the selectivity of the dermatitis for certain persons. The authors' patients acquired a hypersensitiveness to hexamethylenamine after repeated contact with the irritant.

REFLEX ITCHING IN ASTHMA. RAY M. BALYEAT, J. A. M. A. **92**:873 (March 16) 1929.

In 13 of 420 cases of asthma studied, the author elicted a history of itching in the upper part of the chest. The itching and in one case burning were confined to the interscapular region and to the region beneath the clavicles anteriorly on both sides of the chest. It is thought that in these cases the sensory cells in the ganglion of the posterior root receive the impulse; it is then continued upward in the cord through intercalated neurons, and is transferred to sensory spinal nerves in the cervical segments. The areas affected by this viscerosensory reflex are supplied by the third, fourth and fifth cervical nerves. This referred pain can be controlled by pressure and not by scratching.

STUDIES IN ASTHMA. VI. ECZEMA: ITS RELATION TO ALLERGY. EDWARD S. O'KEEFE and FRANCIS M. RACKEMANN, J. A. M. A. **92**:883 (March 16) 1929.

The authors take up eczema in children and eczema in adults separately. Two hundred and thirty-nine children were studied. In 95 per cent of these, the onset of the eczema was before the end of the second year; and it was slightly more common among boys. Skin tests were positive in about 50 per cent of the children, with a preponderance of the reactions due to eggs, wheat and milk. There was marked improvement after elimination of these articles from the diet; even 38 per cent of the test-negative patients improved, when these articles were removed from the diet empirically. Apparently breast feeding had no effect on the course of the disease. Allergic manifestations were found in the family histories of 28 per cent of the children and in 37 per cent of the adults.

The causes of eczema in adults are listed as extrinsic, intrinsic and unclassified. The latter forms the largest and most troublesome group. Extrinsic causes were found in 31 per cent of the adults. Toxic and metabolic causes are considered unimportant.

The association of eczema with asthma, hay-fever and hives was of course noted in a high percentage of adults. "Cures" were obtained in 18 per cent of adults. The importance of a good hygienic background and elimination of ordinary irritating substances is stressed.

TULAREMIA FROM OPOSSUMS. J. A. MEASE, JR., J. A. M. A. **92**:1042 (March 30) 1929.

A case is reported of ulceroglandular tularemia. Symptoms appeared just fourteen hours after skinning opossums. The patient developed a generalized macular rash with vesiculation and desquamation of the hands and feet.

RATTNER, Chicago.

CONGENITAL ECTODERMAL DEFECT. H. MACKAY and A. M. DAVIDSON, Brit. J. Dermat. **41**:1 (Jan.) 1929.

Mackay and Davidson report four cases of this disorder and point out the fact that minor grades of the condition unquestionably pass unrecognized. The cases presented occurred in a woman, aged 32 years, and her two sons and one daughter aged 6, 11 and 13 years, respectively. The defects in each case were present from birth, and the abnormalities in the family group examined were uniform. The woman's mother, one sister, her grandfather and her great grandmother presented similar symptoms. There was marked hypotrichosis, especially of the hair of the mother's scalp. The eyebrows, eyelashes and lanugo hair were also involved in all of the group. All of the nails were dwarfed, roughened, thrown into ridges and presented hyperkeratosis of the nail-bed. No changes were noted in the teeth, and the integument apparently had its full complement of sudoriferous and sebaceous glands. Three photographs accompany the article.

THE CHLORIDE CONTENT OF THE WHOLE BLOOD IN ECZEMA. N. BURGESS, Brit. J. Dermat. **41**:6 (Jan.) 1929.

Burgess reviews the literature indicating the possibility of disturbed chloride metabolism in eczema, and investigated the chloride content of the whole blood in cases included in this group and in certain other diseases of the skin. In his work the chloride content of the whole blood was estimated by the method of Whitehorn. Investigations were made in normal persons and persons suffering from acne, generalized pruritus and pemphigus, as well as in those with eczema. The estimations of the blood chlorides in all these conditions were within normal limits, and high or low values could not be correlated with any clinical type. In view of these observations Burgess states that there appears to be no indication for attempting to reduce the chloride content of the blood in the treatment of these diseases. Tables presenting the blood chloride values in five normal persons, ten patients with various dermatoses and twenty with eczema, accompany the article.

NOTE ON MOLLUSCUM CONTAGIOSUM MILIARE. A. WHITFIELD, Brit. J. Dermat. **41**:10 (Jan.) 1929.

Whitfield presents the records of three cases of a type of molluscum contagiosum which is extremely rare in his experience and to which he gives the suffix "miliare." All three cases were in women, between the ages of 38 and 45. The lesions were very numerous, and appeared on the back, as small more or less acuminate red papules, apparently at the sites of the pilosebaceous follicles, but closer examination revealed that they bore no relation to the follicles. Each lesion had a tiny, translucent center, seen only with a strong lens, which on puncture and expression gave some gelatinous material which, on microscopic examination, proved to be a very small mass of molluscum bodies.

RECOVERY IN A CASE OF PEMPHIGUS FOLIACEUS. R. C. LOW, Brit. J. Dermat. **41**:12 (Jan.) 1929.

Low reports recovery in a typical case of pemphigus foliaceus in a man, aged 22, seen within a fortnight of the onset of his condition and treated with liquor arsenicalis, 3 minims (0.18 cc.), three times a day, 1 per cent ichthyol zinc paste and daily baths of weak potassium permanganate. Cultures of the skin revealed *Staphylococcus albus,* but no *Bacillus pyocyaneus,* and Low raises the question whether the absence of *Bacillus pyocyaneus* does not indicate a milder form of pemphigus.

WIEN, Chicago.

ERYTHEMATOUS ERUPTION DUE TO VANILLA. LORTAT-JACOB and SOLENTE, Bull. Soc. franç. de dermat. et syph. **36**:9, 1929.

A description of a punctiform and patchy generalized erythema due to vanilla is given. The patient was a worker in a candy factory.

THE DANGERS IN THE LOCAL APPLICATION OF THALLIUM ACETATE. R. SABOURAUD, Bull. Soc. franç. de dermat. et syph. **36**:12, 1929.

For many years, ointments containing thallium acetate have been used locally for hypertrichosis. Sabouraud, who has used this method, says that permanent alopecia is not produced, though there is a thinning and atrophy of the hair. The application must be cautiously employed as cases of systemic toxemia (peripheral neuritis and paralysis) have been observed when considerable areas are freely anointed.

LOSS OF IMMUNITY IN SYPHILIS. HISSARD, Bull. Soc. franç. de dermat. et syph. **36**:18, 1929.

A syphilitic patient presented three primary lesions in the course of ten years. Only a moderate amount of treatment had been given for the first two infections, which had become generalized.

NEURODERMATITIS AND EMOTIONAL CRISIS. L. CHATELLIER, Bull. Soc. franç. de dermat. et syph. **36**:27, 1929.

A patch of this disorder appeared shortly after the sudden death by poisoning of the patient's husband.

THE DIAGNOSIS OF PITYRIASIS ROSEA. VEYRIERES, Bull. Soc. franç. de dermat. et syph. **36**:28, 1929.

In questionable cases, daily sulphur baths will have no effect on the lesions of pityriasis rosea, while those of parakeratoses psoriasiformis (Brocq), often confounded with it, will disappear.

THE INCREASE OF SYPHILIS IN PARIS. GOUGEROT and BURNIER, Bull. Soc. franç. de dermat. et syph. **36**:29, 1929.

The figures of the authors show a constant increase in the number of cases of syphilis. Prostitutes were responsible for about 67 per cent of the new cases seen at St. Louis Hospital during 1928.

ARSENIC-RESISTANT SYPHILIS. M. PINARD, P. VERNIER and VERSINI, Bull. Soc. franç. de dermat. et syph. **36**:34, 1929.

The patient was seen in the primary, serologically negative stage of syphilis. Despite intensive treatment with neoarsphenamine he developed secondary cutaneous and buccal lesions. These finally yielded to large doses of the drugs. An interesting transformation took place in the syphilids. They gradually changed into true psoriatic lesions.

VITILIGO FOLLOWING ERYTHEMA NODOSUM. DE LAVERGNE and WEISS, Bull. Soc. franç. de dermat. et syph. **36**:37, 1929.

The authors described a case of vitiligo which took on renewed vigor after the patient experienced an attack of erythema nodosum. The patient showed some evidence of pulmonary tuberculosis, and the authors suggest that the combination of infections, perhaps acting through the endocrine apparatus, played a rôle in the rapid evolution of the vitiligo.

CUTANEOUS METASTASES FROM A SARCOMA DEVELOPING IN A WOUND OF THE HEEL. DROUET, Bull. Soc. franç. de dermat. et syph. **36**:41, 1929.

In a patient, aged 27, there occurred a sarcomatous degeneration of a chronic ulcer of the heel. Cutaneous sarcomatosis followed. The age of the patient and the sequence of events give interest to this case.

COEXISTENCE OF ENDOCRINE, VASCULAR AND CUTANEOUS STIGMAS IN A CONGENITAL SYPHILITIC PATIENT. SPILLMAN, J. HAUSHALTER and WEISS, Bull. Soc. franç. de dermat. et syph. **36**:43, 1929.

The patient, aged 24, presented a gumma, marked varicosities, hypothyroidism and acroasphyxia. Improvement of the systemic and cutaneous disturbances followed the institution of antisyphilitic therapy.

PROPHYLACTIC TREATMENT OF SYPHILIS. L. SPILLMAN and WEISS, Bull. Soc. franç. de dermat. et syph. **36**:44, 1929.

After a short discussion of the general principles underlying preventive treatment, the authors report a case in which a primary lesion appeared despite several injections of arsphenamine. Treatment was begun about fifteen days after the suspected contact. This case shows that a delay of this length of time, or even shorter, between the contact and the institution of treatment may not prevent development of the disease.

CONGENITAL SYPHILIS AND JUVENILE PSYCHOPATHIES. J. HAMEL and P. L. DROUET, Bull. Soc. franç. de dermat. et syph. **36**:49, 1929.

The authors studied the influence of congenital syphilis on the development of juvenile delinquency and mental disease. They conclude that syphilis is the greatest cause of these juvenile disorders. Neuropathy is often only the mask of a syphilis of the second or third generation. Among juvenile criminals, 75 per cent were congenitally syphilitic.

MICHAEL, Houston, Tex.

DERMATOLOGIC ABSTRACTS

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

TANNIC ACID TREATMENT OF BURNS: END-RESULTS IN 114 CASES COMPARED WITH 320 TREATED BY OTHER METHODS. F. BEEKMAN, Arch. Surg. **18**:803 (March) 1929.

The technic of the tannic acid treatment, as carried out in the children's surgical service of Bellevue Hospital, is similar to that laid down by Davidson in August, 1925, except that a 5 per cent solution has been used and the same solution has been applied to burns of the face, instead of the tannic acid ointment, without injurious results to the eyes. Beekman says that recently, in the treatment of patients, particular attention has been paid to the early administration of fluids, in order to prevent blood concentration. The most effective manner of administering the fluids is by hypodermoclysis of a 5 per cent dextrose solution. Additional fluids may be given by mouth and by rectum. A good working rule is that in twenty-four hours a patient should take at least 1 liter of fluid for every 25 pounds (11.3 Kg.) of body weight. Opiates should be used sparingly, as their action of lessening secretions is a contraindication to their use. The mortality has been decreased from 28 to 15 per cent in a series of 434 cases of burns in children. This decrease of mortality is the result of lowering the death rate from toxemia by two thirds. The greatest mortality from toxemia occurs in the period of time between the end of the first twenty-four hours and the end of the third day. The average stay of patients in the hospital was increased six days by the tannic acid treatment. This is probably the result of the fact that patients with severe burns lived who otherwise would have died.

TREATMENT OF ACTINOMYCOSIS. H. CHITTY, Brit. M. J. **1**:347 (Feb. 23) 1929.

Chitty reports four cases of actinomycosis in which a cure was effected by giving 5 minims (0.3 cc.) of tincture of iodine in milk three times daily.

EPIDEMIOLOGY OF SMALLPOX. A. J. H. RUSSELL and E. R. SUNDARARAJAN, Indian J. M. Research **16**:559 (Jan.) 1929.

According to Russell and Sundararajan it is probable that in India low relative humidity consequent on conditions following failure of the periodic rains produces conditions favorable to the development of virulent smallpox. By noting changes in relative humidity, especially in dry areas, this indicator can be used to forecast epidemics of smallpox well in advance.

PEMPHIGUS NEONATORUM. F. G. COLLINS and H. CAMPBELL, Lancet **1**:227 (Feb. 2) 1929.

After reviewing fifty cases Collins and Campbell conclude that pemphigus neonatorum is a contagious disease rarely seen later than four weeks after birth. The infection is probably conveyed from one infant to another through the agency of the physician, midwife, or other attendant. There are two distinct types of the disease: (*a*) a mild type, causing little general disturbance; (*b*) a severe type, which tends to end fatally. The first appearance of the rash is most often

on the groins. The disease seems to attack healthy infants, but shows a predilection for those born and living under unhealthful conditions of space, light and air. The specific organism has not been isolated, but the presence of the staphylococcus in the blister fluid has been demonstrated in a majority of the cases. A mixed infection may supervene and cause death. The best form of treatment is to keep the affected area dry and aseptic; no moist preparation should be used. Any midwife or physician who has been in contact with the disease should not attend another confinement until thorough disinfection of both person and belongings has been carried out. The disease should be made notifiable and, when necessary, mother and infant should be isolated.

PREVENTION AND TREATMENT OF ANAPHYLACTIC SHOCK IN ARSENOTHERAPY BY INJECTION OF CESIUM EOSINATE. GOUGEROT, PEYRE and BERTILION, Ann. d. mal. vén. **24**:81 (Feb.) 1929.

To prevent anaphylactic shock in arsenotherapy, Gougerot and others dissolve the arsenical preparation to be used in from 5 to 20 cc. of a 10 per cent solution of cesium eosinate, immediately before its administration. For the treatment of the anaphylactic reaction they inject from 5 to 10 cc. of the same solution of cesium eosinate intravenously. Both methods proved to be efficient; they failed to get good results in only three of the fifty cases reported. They think that the anti-anaphylactic effect of the cesium eosinate is due to its property to inhibit the blood flocculation (which last is the cause of anaphylactic shock), and therefore it may also be used with the same results in anaphylactic reactions occurring during treatment with mercury or bismuth.

LOCALIZED PREMALLEOLAR CELLULITIS (BOULE PREMALLEOLAIRE). L. DUVERNAY, J. de méd. de Lyon **10**:63 (Jan. 20) 1929.

Duvernay describes a peculiar form of limited cellulitis that is observed only in women and especially in those with a gouty diathesis or with some degree of hepatic insufficiency. It occurs in the form of a limited symmetrical swelling on the anterior aspect of both external malleoli, sometimes extending to the retromalleolar region, varying in size between a nut and a hen's egg, painless, and not interfering with the movements of the feet. On palpation it gives the impression of a lipoma. It has a tendency to increase during exercise and to decrease at rest. After death it disappears completely. A pathologico-anatomic examination of such a swelling excised during operation showed a simple proliferation of the connective tissue, without any inflammatory reaction. The author thinks that it is due to the modification of the arch of the foot and to the chronic traumatism of the malleoli caused by the wearing of high-heeled shoes. The treatment consists in the wearing of shoes with broad low heels, massage and local compression with a rubber bandage.

TREATMENT OF LUPUS ERYTHEMATOSUS WITH BISMUTH. J. NICOLAS, J. LACASSAGNE and J. ROUSSET, Paris méd. **1**:62 (Jan. 19) 1929.

Nicolas et al. report seventeen cases of lupus erythematosus cured by intramuscular injections of bismuth hydroxide. The treatment was well tolerated and rapidly curative Subjective symptoms (itching, burning) disappeared after a second injection; after two more injections the scales and redness began to disappear, and after from eight to fifteen injections the skin became normal. There were observed only three recurrences, in a considerably attenuated form, and rapidly cured by a few more injections. The authors think that this treatment of lupus erythematosus is far superior to any other treatment, including the use of arsphenamines.

TREATMENT OF HERPES ZOSTER WITH NEOARSPHENAMINE. G. MILIAN, Paris méd. **1**:74 (Jan. 19) 1929.

Milian reports five cases and mentions three more cases of herpes zoster in which he observed a complete disappearance of severe pains in from three to

four hours after a hypodermic injection of neoarsphenamine. The disappearance of the eruption followed in a few days. A second injection was only seldom necessary. Only in one case was there exaggeration of all symptoms after the first injection, followed by a rapid cure after a larger dose of neoarsphenamine. Only one of the patients had syphilis; thus the effect of the treatment did not imply the syphilitic origin of herpes zoster. But the author thinks that the therapeutic effect of neoarsphenamine, similar in syphilis, malaria and herpes zoster, suggests the possibility that the as yet unknown pathogenic micro-organism of herpes zoster may be of the class of either spirocheta (as in syphilis) or protozoa (as in malaria).

PRURIGINOUS FORM OF SCARLET FEVER. L. LORTAT-JACOB, Presse méd. **37**:267 (Feb. 27) 1929.

Lortat-Jacob tries to isolate a new atypical form of scarlet fever (pruriginous). It is a benign form, usually without any pharyngeal disturbances of merely slight dysphagia and some redness of the pharynx on the eve of the eruption. The pulse is accelerated (up to 100), not corresponding with the normal temperature that usually is observed during the disease, after a slight initial rise in the temperature (from 37.8 to 38.5 C., or 100 to 101.3 F.); a typical scarlatiniform skin eruption is accompanied by severe pruritus, with exacerbation at night and after the ingestion of hot drinks or food; the desquamation is slight. Because of the pruriginous eruption and the absence of fever and of pharyngeal symptoms, the disease is apt to be mistaken for some noncommunicable scarlatiniform skin disease, as it was in the case reported by the author, in which another, nonisolated child of the family was infected and developed typical scarlet fever.

ULTRAVIOLET RAY THERAPY FOR INFANTILE ECZEMA. K. HULDSCHINSKY, Klin. Wchnschr. **8**:71 (Jan. 8) 1929.

Huldschinsky found that silver therapy in combination with quartz lamp irradiation was effective in the treatment of infantile eczema. His method was as follows: A 3 to 5 per cent solution of silver is brushed on the eczematous area. This application is either left to dry or, while still moist, is exposed to the quartz lamp at a distance of from 50 to 15 cm.

PROGNOSIS IN SYPHILIS FROM THE POINT OF VIEW OF ANTISYPHILITIC TREATMENT. M. TIÈCHE, Schweiz. med. Wchnschr. **59**:25 (Jan. 12) 1929.

To determine the value of the different methods Tièche compared the patients who received treatment with those who received no antisyphilitic treatment. He regards mercury as being mostly a palliative agent. Good results which were seemingly effected by it were generally self cures. Concerning arsphenamine therapy, he feels that it has been overvalued. In some types of syphilis it seems to have no effect. His own observations proved that the prospects of cure are best if the disease is still in the primary stage. He is of the opinion that, if it is possible to commence the treatment before the Wassermann reaction becomes positive, that is, before the spirochetes spread through the whole organism, the prognosis is favorable. Tièche and his assistants treated patients who according to the anamnesis had contracted the disease from thirty to forty days previously. A combination therapy of mercury and arsphenamine was used. Of sixty-one patients treated, sixty gave a negative Wassermann reaction from two to eleven years later. To prove that they were really cured, the author points out that the Wassermann reaction was negative, spermatozoa and blood caused no infections in animal experiments and syphilitic skin eruptions or nervous disturbances were not observed later. Patients who married neither infected their partners nor the offspring. Tièche also points out that defective antisyphilitic treatment is more dangerous than no therapy at all. He also advises against excessive treatment. Concerning bismuth therapy, he feels that it will require several years before a proper evaluation is possible.

Society Transactions

BROOKLYN DERMATOLOGICAL SOCIETY

ARTHUR M. PERSKY, M.D., *Secretary*

Regular Meeting, Nov. 19, 1928

WILLIAM H. BEST, M.D., *Presiding*

SYPHILITIC REINFECTION. Presented by DR. CHARGIN.

Mrs. O. S., aged 28, a saleswoman, was first seen eleven years previous to the present illness, when she presented an initial lesion in the anal fold, a maculopapular eruption and the typical adenopathy. She received five injections of arsphenamine and several injections of mercury. Thereafter she became irregular in attendance, but all the Wassermann tests taken in November, 1917, and in April, May, June and September of 1918 proved negative. On March 13, 1919, she received a small dose of arsphenamine as a provocative, which was followed by a negative reaction to the Wassermann test in March and another in April. Tests made on Sept. 3, 1919, March, 1920, and November, 1923, were negative. In all, eleven Wassermann tests over a period of six years gave negative results.

She did not return to the clinic until a week prior to presentation, when she presented a sore (chancre?) on the labia and a generalized annular eruption. The Wassermann test was positive. She stated that the eruption was of two months' duration.

DISCUSSION

DR. BEST: I should be inclined to think that this is a late rash, held in abeyance for a long period by insufficient treatment. The circinate rash is not customary in early syphilis, except in the colored race.

DR. HECHT: I do not see why a spinal puncture was not done in this case. I understand that an examination of the spinal fluid would be necessary to establish reinfection. There are a few cases in which the condition has been considered as a reinfection, but I do not think there have been sufficient tests made in this case to classify it as such.

DR. WALZER: To say that this patient was cured after a few injections of arsphenamine makes such treatment a wonderful method.

The only thing in the entire history that would help the theory of reinfection is the possible lapse of time between the original lesions and those present at the time of presentation, and we know that even that is of little value. I regard this as a late secondary syphilitic eruption, in spite of the lesions of the mucous membrane.

DR. THRONE: I am inclined to agree that this is late secondary syphilis, rather than a case of reinfection.

DR. CHARGIN: I hesitate to label the case definitely as one of reinfection, but not on account of the reasons expressed. It lacks the history of a definite chancre, which is rarely obtained in women in any event, and a recent Wassermann test taken prior to the appearance of the eruption is lacking. The annular, generalized body eruption may be interpreted as a late macular syphilid, but the papules on the vulva, the palms and the soles are those observed in early syphilis. These points indicate that in all likelihood we are dealing with a reinfection.

PARAPSORIASIS. Presented by DR. FRANK.

R. G., a boy, aged 8, had had the usual diseases of childhood; otherwise his past and family histories were irrelevant.

The illness because of which he was presented began about two years previous to presentation when the child's mother first noticed several small, red, scaly

areas on the body and arms. When the patient was presented, a poorly outlined, discrete, scaly, erythematous eruption, without any infiltration, was present over the trunk and extremities. On the upper part of the abdomen were numerous scaly and lichenified papular lesions with areas of depigmentation.

DISCUSSION

DR. BEST: In this case we find lichenoid lesions with scales on the trunk and scaly plaques on the extremities. Unless we are willing to make two separate diagnoses—psoriasis guttata, and seborrheic dermatitis—one must be accepted which will embrace all these lesions. I think by accepting the diagnosis of parapsoriasis we can explain all the lesions as manifestations of one disease.

DR. ABRAMOWITZ: It is difficult to say definitely whether this child has psoriasis, seborrheic eczema or parapsoriasis. The scaling and bleeding points, with the numerous lesions on the face, do not suggest parapsoriasis. The numerous oval, scaly and lichenified papular lesions on the trunks, with patches of depigmentation, may be in favor of the diagnosis of parapsoriasis. It is possible for leukoderma to develop after other dermatoses, including psoriasis.

DR. THRONE: I should say that the condition is parapsoriasis. I cannot see psoriasis at all in this case. I never saw psoriasis per se cause leukoderma.

DR. GAUVAIN: I agree with the diagnosis of parapsoriasis.

DR. WALZER: I think this is a case of parapsoriasis for the following reasons: While the lesions look psoriatic, there is a lack of typical scaling. There is a lack of the typical punctate hemorrhage. There is a lack of infiltration. The lesions on the thighs are more seborrheic than psoriatic—occurring in thin patches.

Regarding the leukoderma, I am more inclined to favor a suggestion that these patches are normal areas with hyperpigmentation surrounding them.

DR. CHARGIN: I hesitate to make a definite diagnosis in this case, but it does not impress me as being parapsoriasis. I think one is too apt to make this diagnosis which, after all, is a comparatively uncommon one.

Although not characteristic of psoriasis, most of the points favor this diagnosis as against parapsoriasis. It is hardly an eczema in the usual sense; however, it may be seborrheic eczema. The definite diagnosis must be left open for the present.

DERMATITIS MEDICAMENTOSA (PHENOLPHTHALEIN). Presented by DR. WALZER.

E. P., a man, single, aged 24, gave a definite history of hypersensitiveness in the family—his father and an uncle had asthma and a sister had dermatitis venenata.

The condition for which the patient was presented had been present about ten days and followed the ingestion of two tablets of "ex-lax." The patient, however, claimed that attack had occurred nine months previously and another two months before presentation. In both instances he had taken no preparation containing phenolphthalein.

The eruption was located on the back of the fingers, soles of the feet, the upper and lower lips, the tongue and the glans penis. The lesions on the skin were all typical eruption produced by phenolphthalein, that is, violaceous patches, varying in size from that of a dime to that of a dollar. Some of them had a central bulla. None of them were infiltrated.

The eruption on the tongue was pronounced, more so than in any other location. It consisted of erosions.

URTICARIA FACTITIA. Presented by DR. BEST.

J. B., a white man, aged 21, an American, a clerk, said that five years prior to presentation the slightest trauma, such as friction, would produce large, edematous, itchy swellings which would completely disappear in half an hour or so. The patient was otherwise in good health.

DISCUSSION

DR. WALZER: Urticaria factitia or dermographism has until recent years been considered a nervous phenomenon. It was, in fact, described by the French as a manifestation of hysteria. Recent investigation, however, has demonstrated that the factitious wheal is a definite pathologic entity—that it is a real wheal with the pathologic changes of a mild acute inflammatory process, not a simple dilatation of the vessels with mechanical exudation.

Dermographism is not, in all probability, a neurologic phenomenon, since trauma apparently liberates a substance that is the cause of the wheal; at present, it is not universally accepted that a person can become sensitive to an organization wholly within itself. That there may be different types of dermographism was demonstrated a year or so ago. We showed that certain such patients possessed in their blood serum a substance which in local passive transfer to the skin of a person used as a control produced a certain change at the sites of injection. Later on wheals developed at these sites of injection.

DR. CHARGIN: This condition is not often associated with urticaria. We have treated many of these patients, all without success. I recall one patient whom we treated by a variety of methods over a period of two years, and who recovered spontaneously about six months after all treatment was stopped. The point that I want to make is that treatment is not often successful, and that those who recover do so spontaneously.

DERMATITIS VENENATA (PLASTER OF PARIS). Presented by DR. PERSKY.

E. N., aged 33, had had tuberculosis of the lumbar vertebrae for almost five years. She had been wearing a plaster of paris cast for four months. The eruption began soon after the cast was applied.

Almost the entire trunk, except for a well defined space running longitudinally over the abdomen where the cast was laced, was affected. The lesions were brownish and erythematous, oval and irregularly shaped, scaly macules. He eruption was almost confluent over the abdomen. The upper and lower borders corresponded exactly to the outline of the cast. Scrapings taken from the lesions showed no fungi. When the patient left the cast off for two days, the eruption completely disappeared, only to recur again when it was applied.

DISCUSSION

DR. GAUVAIN: When I first saw this patient, three weeks before presentation, that portion of her torso which had been covered by the cast showed hundreds of perfectly round discrete lesions about the size of a pea, or slightly larger. There was slight exfoliation, and the lesions were pink. I also observed that in the depression over the lumbar spine, where the cast did not exert pressure on the skin, and in the interval between the two sides of the cast, about 3 inches (7.62 cm.) wide, in front, there were no lesions. The patient has always worn a silk shirt under the cast. At this first observation a diagnosis of tinea versicolor was made, but the microsporon was not found.

When I saw the patient about two weeks later she said that she had been ill, in bed and had not worn her cast. She said the eruption had disappeared, when she left the cast off, but had returned on about the second day when she started wearing the cast again, this time without the erythema. It seems to me that this condition has always been a tinea versicolor with erythema present at first because of irritation from the cast; that the disappearance of the eruption during her illness was not actual, but relative, and that we should be able to find the microsporon on further examination. I cannot believe that a plaster dermatitis would give so many perfectly circumscribed spots of nearly uniform size.

DR. ABRAMOWITZ: When tinea versicolor is on the mend, it is sometimes difficult to find the microsporon. If it has not already been done, I should suggest the examination of the lesions through the Woods' filter. The lesions show up as a golden brown fluorescence.

DR. CHARGIN: For the reasons already given by the various speakers, I think we must regard this as tinea versicolor.

DR. BEST: I cannot conceive of a tinea versicolor limited absolutely to the areas with which the cast comes in contact. In the front where the cast does not meet there is an area about 2 inches (5.08 cm.) wide without a single lesion, and in the back where the cast does not touch the skin there are no lesions. Of course, fungi would grow more readily where there is warmth and moisture, but it seems to me there would be some lesions of tinea beyond the margins of the cast and under the cast where it does not come in actual contact with the skin.

A CASE FOR DIAGNOSIS (SPOROTRICHOSIS?). Presented by DR. GRAHAM.

L. R., a white boy, aged 14, was born in Louisiana and lived there until June, 1928, when he came north. In 1920, the patient cut himself over the inner side of the ankle with a knife. Iodine was applied, and the wound apparently healed without infection. About three weeks later, he noticed about nine or ten small, hard lumps on the medial and posterior sides of his leg, in linear arrangement. They were not painful, but the patient scratched them, and they became ulcerative and bled. Various ointments were applied without relief.

At the time of presentation there were noted on the inner aspect of the left leg, extending from a point midway between the heel and toe up to the knee, ten lesions, all of the same character, each one separated from the other by apparently normal skin. The lesions were sharply defined, verrucous, and at times moist and exuding a thin seropurulent material. The lesions, which varied in size from 5 mm. to 3 cm., seemed to follow the lymph channels which drained this area.

The boy had been getting potassium iodide in ascending doses, and the lesions had dried up and appeared cleaner; otherwise the administration of the drug had little effect. Three weeks before presentation, the three lower lesions on the ankle were given two skin units of unfiltered roentgen-rays, the lesions being closely screened. There was no change as a result of this treatment.

Two cultures were made on Sabouraud's mediums, one from fresh material and one from material dried three days at room temperature. The fresh culture showed staphylococci and streptococci, but no fungi; the dried culture showed no growth of any kind.

A biopsy was done, a report of which follows:

Sections of the lesions showed them to be warty thickenings of the skin, with thick scales covering the surface. In the thickened skin there was a polymorphonuclear reaction, and in places a purulent exudate between the superficial epidermis and the scales. In this purulent exudate numerous short chains of streptococcic organisms were noted. There was a subacute inflammatory reaction about the vessels of the corium. No fungi or branching organisms were apparent in sections stained with Giemsa.

Photographs and sections of the lesions were shown to Dr. Frank Fraser of the Dermatology Department of Cornell. He ventured the opinion that the lesions were those of lichen planus (verrucous type).

DISCUSSION

DR. BEST: We have only a few things to consider. Blastomycosis is usually a confluent solid patch, and more or less purple; while tuberculosis verrucosus cutis, it seems to me, would have been recognized readily by the pathologist. This condition spreads along the lymphatics and breaks out at intervals; so I can think of nothing other than sporotrichosis as the diagnosis.

DR. THRONE: I cannot conceive of lichen planus looking like this. I never saw lesions in a case of lichen planus discharge or appear like these. The fact that the mycotic organism was not found on culture does not necessarily rule out a mycotic infection. Clinically, I think it is sporotrichosis.

A CASE FOR DIAGNOSIS (PYODERMIA?). Presented by DR. BEST.

J. H., a white man, aged 32, an American, a printer, noted about ten weeks previous to presentation several discrete split-pea-sized blebs on each side of

his chin. The lesions spread down over the neck within a week or ten days, and partly cleared up within the next four or five days with treatment which the patient believed was mercury ointment. Every few days a new crop of similar blebs would break out on different parts of the body. The full quota of lesions in any given area would appear within twenty-four hours. With the appearance of each crop of lesions there was severe burning of the part, which later became itchy. The lesions dried up into crusts and exfoliated in a week, but new crops appeared, sometimes in the same area, even before the old crop had entirely exfoliated.

He had always been in good health previous to the present illness. Just prior to the onset of the illness his daughter had had an attack of impetigo, which cleared up under local treatment in about ten days.

Examination showed vesicles and vesicopustules, some circinate in arrangement, some with central crusts simulating impetigo lesions. Some of the lesions were single and the size of a split pea, while others were circinate, approximating the size of a dime or slightly smaller. The rash was most profuse on the back of the neck and the right axilla with a few lesions on the dorsum of the hands, groins and scrotum. There was pigmentation on the forearms and feet, especially the soles, at the site of old lesions which had entirely healed. In the axilla and on the back of the neck where the lesions were most profuse there was some evidence of grouping, but on the hands, groins and scrotum the lesions were distinctly single and isolated. The trunk, arms and thighs had at all times been free from lesions.

DISCUSSION

DR. ABRAMOWITZ: Impetigo, I think, can be ruled out. I am not acquainted with any form of it that is accompanied by the symptoms that this man presents. The early tendency of these lesions to become pustular is not in favor of dermatitis herpetiformis. There is the possibility of impetigo herpetiformis. The latter disease is extremely rare in this country and is usually accompanied by severe constitutional symptoms. The third possibility and the one I am in favor of is a type that has been occurring with increased frequency during the past few years. It is characterized by relapsing pustular and pemphigoid lesions, due to a virulent streptococcic infection, and seems to subside under streptococcus vaccine.

DR. THRONE: I am inclined to agree with Dr. Abramowitz that it is a pyodermia — simply a virulent type of skin infection.

DR. GAUVAIN: The eruption in this case seems to be somewhat confusing. Some of the lesions on the face are distinctly those of impetigo; however, others which evidently began in the same way are ulcerated. On the back of his neck are some groups of vesicles on an erythematous, edematous base, which, viewed alone, would distinctly be called herpes zoster. The diagnosis of dermatitis herpetiformis is the best that I can offer, although it is not a classic picture of this disease.

DR. WALZER: I shall call this a case of pyodermia. I should rule out dermatitis herpetiformis because of the absence of pruritus, grouping and duration of the disease.

MANHATTAN DERMATOLOGICAL SOCIETY

DAVID L. SATENSTEIN, M.D., *Secretary*

Meeting, December, 1928

LUDWIG OULMANN, M.D., *Chairman*

A CASE FOR DIAGNOSIS. (NEUROTIC EXCORIATION.) Presented by DR. ROSEN.

M. L., aged 21, born in the United States, from the Post-Graduate Skin Clinic, said that three years previously a sore had appeared on the skin which disappeared in about two weeks after discharging a little pus. Nothing further was

noticed until about four months prior to presentation; then the skin became red at the same site, and discharged a bloody serum. This discharge ceased in about three weeks, and the lesion was covered with a small scab. The discharge started again a few days prior to presentation.

The patient had a punched out, deep ulcer, the size of a dime, on the left side of the chin. There was a thick bloody serum at the base.

DISCUSSION

DR. ELLER: I think that this man presents a dermatitis artefacta. It does not look like any definite entity. It has an artificial appearance. The patient presents some anesthesia of the cornea and some anesthesia of the throat. It is probably a dermatitis artefacta due to a compulsory neurosis.

DR. WISE: I agree with Dr. Eller. I think that dermatitis artefacta is the most acceptable diagnosis. However, we should not dismiss the case as being certainly one of dermatitis artefacta without further investigation. I once observed a patient infected with *Bacillus mallei,* who had a lesion closely resembling this.

DR. MACKEE: I agree with Dr. Eller. The lesion presented simulates a number of diseases, gumma, for example, or tuberculosis, but it is also characteristic of the dug out excoriations of Colcott Fox, falling under the head of neurotic excoriations in contradistinction to those of malingering. I think Dr. Eller had in mind that the patient probably has a compulsory neurosis and if adequately interrogated would disclose that he manipulates the lesion, and tell why. The patient is not deceptive; he is not trying, as a malingerer would to hide the fact that he is producing these lesions. Until this question has been done one cannot be certain whether to make a diagnosis of neurotic excoriations or malingering. These dug out lesions simulate a number of conditions. I have seen them resembling serpiginous ulcerative syphilid, rodent ulcer, roentgen ulcer, tuberculid, etc. The reason I think that in this case we are dealing with neurotic excoriations is that we have, first, an indolent ulcer, the type one gets in chronic radiodermatitis. There are a number of peculiar scars on the face that are not likely to have been left by any disease entity. The linear scars scattered over both cheeks, as well as the round scars of former ulcers, impress me as representing neurotic excoriations. It is necessary, of course, to rule out syphilis and other diseases before a positive diagnosis of neurotic excoriations can be made, unless the patient admits traumatism.

DR. FRASER: I agree with Dr. Eller that the lesion is dermatitis artefacta. The healed lesions do not present the appearance of fine tissue paper which is characteristic of syphilis.

DR. GILMOUR: I agree to neurotic excoriations as the diagnosis. The only other thing I can think of is syphilis, in a form I have never seen. The question of treatment therefore comes up. If he has not had antisyphilitic treatment that would, I think, be my line of procedure.

DR. ELLER: There are two types of neurotic excoriations — those of the malingerer who attempts to hide his malingering and those of the patient who mutilates the skin because of an uncontrollable desire to do so and who readily admits that he does.

DR. MACKEE: Malingering is one thing and neurotic excoriation is another, although they may both be placed under the general heading of dermatitis artefacta. Malingering is a psychosis; neurotic excoriation is a neurosis. A malingerer will never admit traumatizing the skin; the patient with neurotic excoriations readily admits having caused them. The malingerer produces the artefact in order that he may excite sympathy, avoid work or duties, collect insurance, arouse interest, cause professional confusion or error, etc. The person with neurotic excoriations has a compulsory neurosis. He will, when properly interrogated, admit the act and the impossibility, almost, of avoiding it. He will insist that there is something in the lesion that has caused the lesion or that is keeping it from healing or that gives rise to the subjective symptoms, and that this piece

of debris must be removed. In some mild cases, the act may be but a habit, a subconscious impulse, as for instance, in the case of the bald-headed man of middle age who picks unconsciously at his scalp while reading the evening paper. At the other extreme is the patient who brings harmless insects for examination (acarophobia) or pieces of tissue, etc.; then there is the trichotillomania, etc., all of which are in the same category. Patients with neurotic excoriations pick at every elevation above the surface of the skin — milia, comedones, scabs, etc.

DR. ROSEN: I was glad to hear that the majority of the members agree as to the diagnosis of neurotic excoriations. When I first saw this patient the day before at the clinic, this diagnosis did not occur to me. I thought on account of the marked infiltration of the tissues at the base of the ulceration that there was some underlying cause. I believed that the case should be studied bacteriologically, and that a roentgen examination should be made to rule out the possibility of periostitis.

TINEA TRYCHOPHYTINA CORPORIS SIMULATING PSORIASIS. Presented by DR. BECHET.

C. F., a young woman, aged 27, presented dry, rounded, sharply outlined, scaly patches scattered over the arms and trunk. They had been present for a few weeks. Their centers were clear. Scrapings were positive for tinea. The adherent silver scales and the circinate and serpiginous conformations markedly resembled serpiginous psoriasis.

TUBERCULOSIS CUTIS. Presented by DR. BECHET.

F. D., a colored girl, aged 16 years, from the Post-Graduate Skin Clinic, had had a papillomatous, cauliflower-like, verrucous, lobulated growth of two years' duration, involving most of the nose. Several of the lobulated masses were almost as large as the nose itself. Despite a negative Wassermann reaction, the patient had received eight injections of arsphenamine and mercury as a therapeutic test, with no effect on the lesions. A biopsy had confirmed the clinical diagnosis. The patient was shown for therapeutic suggestions. There had been the greatest improvement with repeated paintings of acid nitrate of mercury, as recommended by Adamson. However, after an improvement of about 50 per cent had taken place, that method apparently ceased to be of benefit. The patient had had many exposures to the Kromayer lamp with decompression. Fulguration and trichloracetic acid had been used without signal improvement. The tuberculous process was extending upward toward the eyes. She had also received twelve roentgen treatments in one-quarter skin doses once a week, a method that, in the presenter's experience, was inferior by far to much larger doses properly spaced. While the tuberculous mass had flattened down enormously, as evidenced by the photographs shown, there was still marked evidence of the disease.

DISCUSSION

DR. ELLER: I think that the lesions should be treated by some form of high frequency.

DR. WISE: I think that the treatment with electrodesiccation is probably the best. Massive doses of roentgen rays would have better cosmetic results, however.

DR. MACKEE: As far as concerns local therapy, I agree that the method of election at the beginning, in a case of this kind, would be intensive roentgen or radium therapy. After the fractional treatment given in this case, it would be well to give the patient a rest of several months before instituting intensive roentgen therapy. If the latter fails, then try electrodesiccation. But I do not believe that we should depend entirely on local therapy in a case like this. Of course, it must be admitted that the best results that we get in these cases, with local therapy, are those obtained at the Copenhagen Institute with ultraviolet

radiation (Finsen lamp). We cannot do that here, however. The German school on pulmonary tuberculosis claims good results in pulmonary tuberculosis and in lupus vulgaris with a diet very rich in vitamin and sodium chloride free. This diet is now being tried by Edgar Mayer of Saranac Lake. I think it might be well to try it in this case. Tuberculin therapy is not very efficacious in the ulcerative and hypertrophic types of lupus vulgaris, but it is of service in the nonulcerative and atrophic types, and I think that it is worth trying in this case. It would probably have to be given over a long period of time, probably eighteen months, beginning with 30,000 mg. and advancing by geometrical progression to milligram doses, one dose being given each week. Treatment with a gold compound may be tried, since some claim success with it. Of course, anything that will increase the general health and resistance of the patient will be of great service—generalized heliotherapy, generalized therapy with ultraviolet rays, change of environment, supervised exercise and rest, etc.

DR. SCHEER: As far as local treatment is concerned, I should like to speak favorably of an old fashioned and somewhat neglected method, i. e., the use of pyrogalic acid locally. We had at Mount Sinai Hospital a case of lupus vulgaris extending entirely across the front of the neck, in a space 6 inches long and 3 inches wide and raised ½ inch above the level of the skin, a hypertrophic lupus vulgaris, which was treated with applications of 10 per cent pyrogalic acid. In a week, the entire hypertrophic mass had disappeared. A smooth scar was left, which showed about a dozen small nodules. When it gets to that stage, destruction of the individual small nodules with electrodesiccation is indicated. I should ask Dr. Bechet to try pyrogalic acid and show the patient next month.

DR. OULMANN: In the last number of the ARCHIVES is an article recommending an ointment containing zinc sulphate, which is used for destroying this kind of lesion. It has a selective affect on the diseased tissues and is first used in strong, then in weaker concentration. The reports on such cases of hypertrophic lupus are good.

PUSTULAR SYPHILID IN TATTOO MARKS. Presented by DR. PAROUNAGIAN.

W. D., aged 22, an American negro, was seen first on Dec. 4, 1928. There was a generalized pustular syphiloderm. The Wassermann reaction was four plus. The point of interest in presenting the case was that the patient on his right forearm had a large tattoo mark in the blue part of which the lesions were abundant, whereas in its red portions no lesions were present.

DISCUSSION

DR. OULMANN: This is a typical case of the kind described first by Dohi, in which the lesions appear in the blue part, while in the red part the cinnabar protects the skin against the syphilitic invasion. This is an instructive case.

DR. MACKEE: This patient presents another interesting feature. He has a tubercle of Carabelli and other phenomena which have been held by a number of men in different parts of the world to be pathognomic of congenital syphilis. We have had a number of cases here of the tubercle of Carabelli in patients who had congenital syphilis. Most of us have seen the tubercle of Carabelli in patients free of syphilis so far as could be ascertained. Unless it has been definitely proved that a patient who has syphilis can acquire syphilis, the fact that this man has secondary syphilis would appear to make it unlikely that he has uncured congenital syphilis.

DR. PAROUNAGIAN: In presenting this patient, my sole object was to demonstrate the fact that lesions do not occur in the red portion of a tattoo mark. Even though I noticed that the patient had deformed teeth, a high vault, the tubercle of Carabelli, a protruding forehead, etc., which I consider representative of congenital syphilis, I purposely did not mention these in the history, as I knew the sentiment of the society, in order not to create too much discussion. How-

ever, since Dr. MacKee has called attention to the patient's teeth and expressed a doubt whether persons with congenital syphilis can acquire syphilis, I feel I must say a few words.

The old theory that persons with congenital syphilis cannot contract syphilis is as obsolete as is the statement that once a person contracts syphilis he cannot be reinfected. The fallacy of this has been demonstrated beyond the shadow of a doubt, for I have presented before this society, and also before the academy section, a very large number of cases of superinfection and reinfection. I have also observed a number of patients with acquired syphilis who manifested strong evidence of congenital syphilis.

Several years ago, in the academy section, I presented a young man who had an undisputed case of secondary syphilis. In addition to the secondary lesions, he had a number of large, pigmented scars on the lower extremities, which he stated had been present since childhood. While in the United States Navy, he had sores on his legs that caused the Navy physicians to make a Wassermann examination, the result of which was reported as four plus. They gave him a number of injections of arsphenamine and mercury at a naval hospital, at which he remained for a long time. He also stated that he had been told by some friends and neighbors that his father, who was dead, had had syphilis and had died from the same.

DR. MOUNT: There is a partial substantiation of what Dr. Parounagian says. In experimental work done by Finger, of Vienna, in either 1907 or 1909, on monkeys, it was found possible to produce a second chancre in a monkey about six months after the first chancre, and at this time the internal organs were teeming with spirochetes.

PSORIASIS OF HANDS AND PUBIC REGION. Presented by DR. PAROUNAGIAN.

A. C., an Italian, aged 32, reported to the clinic of the Bellevue Hospital, stating that the involvement of the skin on his hands had first started three years previously. The lesions were most pronounced on the palms and on the pubic region. There was a patch on the occipital region. The rest of the body was entirely free from lesions. The lesions were bright red, scaly, dry and pruritic. The eruption had failed to respond favorably to any form of treatment.

DISCUSSION

DR. WALLHAUSER: I have had experience with two cases of this type, in which the hands were mainly involved. Both cases resisted all the ordinary remedies, including chrysarobin and the roentgen rays, and finally resulted in atrophy and contraction of the hands and fingers, producing the appearance of claw hand. I shall be interested in learning the experience of others with this type of psoriasis.

DR. FRASER: I should like to hear suggestions as to therapy. I have had an experience similar to Dr. Wallhauser's.

DR. MACKEE: My diagnosis is psoriasis. Nevertheless, dermatophytosis and psoriasis can simulate each other so closely as to make a diagnosis exceedingly difficult. I think that a careful bacteriologic examination should be made. Arsenotherapy and generalized ultraviolet therapy might prove beneficial.

DR. OULMANN: Ravogli stated that in his cases of psoriasis in syphilitic patients arsphenamine had a beneficial influence. I have found just the opposite. I have seen a psoriasis flare up or reappear during or right after arsenical treatment.

DR. MACKEE: In a case like this, the psoriasis is not behaving as psoriasis should; in other words, the disease is finding a favorable environment in certain parts of the body and that generally denotes some general systemic condition, either of the circulation or of lowered general resistance, or toxic, etc. These roentgen-fast and therapeutic-fast cases can sometimes be made again amenable

to local therapy by the use of autohemotherapy, anaphylactic shocks, etc. If there is a history of arsenotherapy, it might be well to try sodium thiosulphate.

DR. WISE: My experience in the treatment for psoriasis of the palms has usually been discouraging. I have learned my lesson about roentgen therapy in such cases. Unless roentgen therapy produces a demonstrable improvement, after the administration of two or three quarter units, I do not believe it wise to continue it. In a case of this kind I should agree with Dr. MacKee as regards general therapy, and should also try an intensive course of arsenotherapy by injection; autohemotherapy is sometimes also useful.

I favor the diagnosis of psoriasis, bearing in mind, however, the possibility of dermatophytosis, as mentioned by Dr. MacKee.

DR. MOUNT: My experience has been exactly that narrated by Dr. Wise. If a case does not respond visibly within the first few doses of roentgen therapy it is better to stop it.

DR. ELLER: I also agree with Dr. Wise regarding roentgen therapy. In reference to autohemotherapy, I have tried it in several cases and have had poor results. Injections of bismuth also have been a failure in my hands. I am now trying injections of gold and sodium thiosulphate. My results thus far with the latter have not been promising.

DR. BECHET: I think this would be a good case in which to prove or disprove the theory that Dr. Throne has held, namely, that cases of extensive psoriasis of the hands and particularly of the palms are due to retention of arsenic. I think it would be a good plan to do a quantitative test for arsenic in the urine. In reference to autohemotherapy, Dr. Kingsbury and I, a few years ago, used plain venesection in obstinate cases of psoriasis. We removed about 100 cc. of blood about once or twice a week, and the results were just as favorable as those following autohemotherapy and autoserotherapy.

Dr. Throne does not claim that retention of arsenic is a cause of psoriasis, but he does state that psoriasis limited to the hands is frequently associated with retention of arsenic and is greatly benefited by sodium thiosulphate.

EPIDERMOLYSIS BULLOSA HEREDITARIA. Presented by DR. GILMOUR.

N. S., a white boy, aged 5, had been presented at other dermatological societies by various men. His was a typical case of epidermolysis bullosa hereditaria. On Dec. 4, 1928, a section from the edge of a bulla just below the left knee showed a diminution of elastic fibers in the papillae.

DISCUSSION

DR. FRASER: I saw this case at the Cornell Clinic, and I agree as to the diagnosis of epidermolysis bullosa.

Microscopic sections show elastic fibers in the deep layers of the corium, but there is an absence of these elements in the upper layers and papillae.

Engman and Mook reported absence of elastic tissue in skin remote from the lesions. I suggest another biopsy to determine whether this observation can be confirmed in this case. It is difficult to conceive that loss of elastic tissue alone accounts for the production of bullae. There are probably other factors, such as lack of vasomotor control or some developmental defect, as suggested by MacLeod, in the epidermal cells.

There is an apparent local sensitivity in the skin of these patients, but the exact mechanism involved in the production of the lesions is not clear. Dr. Satenstein has made a histologic study in a number of cases. I should like to hear his views.

DR. OCHS: If it is sensitivity that is hereditary, how do you account for the acquired form?

DR. SATENSTEIN: The specimens that we examined practically all showed changes in the elastic tissue of the entire corium. The fibers in the upper portion

of the corium were practically absent, only a few small bits being present. In active clinical bullous lesions, we find dilatation of the upper vessels and an interstitial edema throughout the entire corium. The edema apparently develops rapidly and the fluid collects at the top of the papillary bodies; the elastic tissue being absent, the epidermis is ripped off from the cutis. The mechanism is purely a physical one and gives the impression of being the result of a developmental defect. I cannot see where the question of sensitization, as described by Dr. Fraser, comes in.

DR. FRASER: I did not mean to convey the impression of sensitivity in the sense that a specific reagin could be demonstrated in the blood. If serum from this boy were injected into another boy, friction or injury of the skin of the second boy would probably not produce the characteristic lesions.

DR. WALLHAUSER: The theory suggested by Dr. Fraser seems to be strengthened by my experience with cases of transitory epidermolysis bullosa in which certain areas are involved, as in a case that came under my observation, in which the hands and face developed blisters from the slightest injury. This patient was a stone-cutter, and developed blisters from flying particles of stone at the point of contact. This sensitiveness continued over a period of years, gradually becoming less, and disappeared entirely as his general condition improved under diatetic and hygienic measures, nor has there been a recurrence over a period of about fifteen years.

CUBA DERMATOLOGICAL ASSOCIATION

J. J. MESTRE, M.D., *Secretary*

Monthly Meeting, Dec. 6, 1928

B. SAENZ, M.D., *President*

LICHEN PLANUS ZONIFORMIS. Presented by DR. SAENZ.

A white woman presented bandlike lesions of lichen planus on both legs and arms. The condition had lasted for three years. There was considerable pigmentation. Pruritus was slight.

DISCUSSION

DR. PARDO-CASTELLO: The papules in this case remind me of those in cases presented before this association under the name of epidermodysplasia verruciformis of Lewandowsky. Of course, I agree with the diagnosis of lichen planus zoniformis, but I wonder if the cases of epidermodysplasia have not some relation with atypical lichen planus, which they really resemble closely. In this case, were it not for some typical papules of lichen planus and their distribution it would be difficult to make the differential diagnosis.

DR. SAENZ: I cannot agree with Dr. Pardo-Castello. The pathologic changes and evolution of epidermodysplasia verruciformis are entirely different from those of lichen planus.

SYPHILITIC CHANCRE OF THE TONSIL. Presented by DR. GRAU.

A white woman, aged 28, was referred from the ear, nose and throat department suffering from a cutaneous rash, which was a typical papular syphilid. The initial lesion had been treated at the throat dispensary and consisted of a deep punched-out ulcer about the size of a quarter. The tonsil was greatly enlarged and congested. The ulcer was covered by a grayish membrane. Enlarged glands were present on the right side of the neck and in the submaxillary region. *Spirochaeta pallida* were found on dark-field examination. Results of microscopic examinations for diphtheria bacillus and Vincent's organisms were negative.

DISCUSSION

DR. FERRER: Extragenital chancres are not so rare as it is supposed. In this case, the diagnosis was more difficult because of the history of recurrent attacks of tonsillitis in the patient.

DR. MESTRE: Has it been possible to find the method of inoculation?

DR. GRAU: The patient has been unable to explain the method of contagion.

LICHEN PLANUS OF THE GLANS PENIS. Presented by DR. SAENZ.

An old, white man, presented a white thickening of the glans penis and of the prepuce, which produced almost a complete phimosis. The condition had been present for three months. There were some small whitish dots on the mucous membrane of the cheeks, near the last molar. No skin lesions were observed.

DISCUSSION

DR. PARDO-CASTELLO: I do not agree with the diagnosis. I think the condition in the penis is leukoplakia.

DR. SAENZ: When I saw the patient the diagnosis was unmistakable. There has been some improvement under treatment with arsenic and radiotherapy of the spine, which favors the diagnosis of lichen planus.

LUPUS VULGARIS. Presented by DR. MESTRE.

A white boy, aged 4, born in Syria, had a raised, semitranslucent yellowish plaque, about the size of a dollar, on the left cheek. The condition had been diagnosed as oriental sore, and had been treated locally with the roentgen rays and ultraviolet light. Finally, the plaque was destroyed with the cautery. The scar of this burn was seen in the center of the lesion in the form of an atrophic surface of 2 cm. Under vitropressure some yellowish nodules were seen in the margin of the plaque. Sections confirmed the diagnosis of lupus vulgaris.

DISCUSSION

DR. SAENZ: I saw this patient about three years ago after his arrival from Syria, and I made the diagnosis of oriental sore. I think the lupus vulgaris developed later on the scar of the primitive lesions.

DR. MESTRE: I should like to know if the diagnosis was proved by the finding of *Leishmanias* and what the treatment was.

DR. SAENZ: The lesions healed under local treatment alone, and the patient also received injections of arsphenamine.

ADENOMA SEBACEUM — BALZER. Presented by DR. SAENZ.

A child, aged 11, had small growths, the size of a millet, on the face for six years before presentation. They were yellowish white and innumerable and were situated on both cheeks and around the nose. Sections showed the typical picture of the Balzer type of adenoma sebaceum.

XANTHOMA TUBEROSUM. Presented by DR. PARDO-CASTELLO.

A white girl, aged 8 months, was the only child of healthy, young parents. About four weeks after the birth of the child, the mother noticed the appearance of small "warts," the size of a pinhead, distributed irregularly all over the body. These lesions increased in size until some of them attained the volume of a filbert. The child was in excellent health. There were no apparent subjective symptoms. On examination, about 150 small tumors were seen irregularly scattered over the entire body; they were purple or of the normal color of the skin, of firm consistency, some seated and some pedunculated, and on pressure under the diascope, a peculiar yellowish tone could be demonstrated. Around the neck the yellow was

marked. Sections showed a magma of conjunctive tissue filled with well differentiated cells filled with droplets of a refringent substance. These cells affected the shape of giant cells, with a crown of nuclei and an enormous cellular body. Chemical examination of the blood showed: sugar, 0.078 and cholesterol, 0.125.

DISCUSSION

DR. FERRER: I wish to thank Dr. Pardo-Castello for presenting this interesting case which is rarely seen. It is important to note the low amount of cholesterol in the blood, contrary to what has been observed in cases of this kind. This makes me believe that the substance found in the xanthoma cells, if proved to be cholesterol, must be taken selectively by these cells from the blood, even in cases in which the amount of this substance in the circulation is normal. I had a patient with xanthoma tuberosum under my care for some time, in whom the cholesterol content was as high as 0.400. This case was interesting because the patient was syphilitic, and I saw the lesions of xanthoma vanish under arsphenamine therapy.

DR. SAENZ: Treatment with insulin might be of benefit, although the age of the patient is not suitable.

LEPROSY. Presented by DR. SAENZ.

The patient had been seen three months previously with an erythematous lesion on the face, of the shape of a crescent, dark red and about the size of a dime. On the external aspect of the right arm, she also had a group of coppery red tubercles, about the size of a small pea, and arranged in circles, suggesting a tertiary syphilid. The Wassermann reaction was negative. Hansen bacilli were found in the nasal mucus.

TUBERCULOSIS VERRUCOSA CUTIS. Presented by DR. FERRER.

A colored boy, aged 17, since he was 10 years old had presented verrucous lesions around the neck, which, in the shape of a circumscribed patch, had first healed in the center, leaving atrophic scars, and had progressed at the periphery in the shape of an eccentric band of circular outline. Similar lesions were seen on the axillae, on the bends of the elbows, in the gluteal regions, in the popliteal spaces, on the knees and on both hands. The lesions were black, raised, hyperkeratotic and dry. Biopsy showed hyperkeratosis, acanthosis and a dermal infiltration constituted by epithelioid and giant cells.

DISCUSSION

DR. FERRER: I should like to know the opinion of the members of the association concerning the points of contact between tuberculosis verrucosa cutis and lupus vulgaris verrucosus and hypertrophicus. In the first case there is, it is said, a bacillary superinfection in a patient whose allergic power is increased, the infection coming from outside. In a case like the one presented by me, the many points of infection and their widespread distribution make improbable the theory stated.

DR. PARDO-CASTELLO: In my opinion, there is no real difference between tuberculosis verrucosa cutis and lupus vulgaris verrucosus. Only in cases of the so-called necrogenica is the local inoculation of the tubercle bacillus clearly proved.

PEMPHIGUS VULGARIS TREATED WITH SODIUM THIOSULPHATE. Presented by DR. PARDO-CASTELLO.

A white man, aged 53, had been admitted to the skin ward of the "Calixto Garcia" Hospital, suffering from chronic pemphigus of five months' duration. Nikolsky's sign was present. The patient had had syphilis and had been treated years before in the hospital. The Wassermann reaction was positive; the blood count showed a 10 per cent eosinophilia, and *Trichocephalus dispar* were found in

the feces. Tentatively and empirically, injections of sodium thiosulphate were administered daily in doses of 1 Gm. in 20 cc. of sterile water. Seventeen injections were given without the slightest disturbance. After four doses the bullae ceased to appear, and those in evolution dried up rapidly. Nikolsky's sign disappeared, and the patient made an uneventful recovery. It is too soon to say whether the remission was due to the treatment employed or whether it was spontaneous.

DISCUSSION

DR. SAENZ: I had the opportunity of discussing this case with Dr. Pardo-Castello, and following his advice I used the same medication in a private case of pemphigus vulgaris chronicus. I have not seen much improvement as yet, although it is too soon to state definite conclusions. My patient is still under treatment.

DR. GRAU: I have treated a patient with pemphigus with sodium thiosulphate with negative results.

MYIASIS OF THE SCALP. Presented by DR. OTEIZA.

A white girl, aged 6, born in Spain, had three furuncle-like lesions on the scalp in which numerous larvae were seen. The larvae were killed with chloroform and extracted with forceps. They were classified as *chrysomyia macellaria.*

JUXTA-ARTICULAR NODULES. Presented by DR. QUERO.

The patient with juxta-articular nodules, presented by Dr. Quero at a former meeting, was cured with diathermy applications. The diagnosis was inflammatory nodules and not juxta-articular nodules of Lutz-Jeanselme.

ATLANTIC DERMATOLOGICAL CONFERENCE: NEW YORK, NEW ENGLAND, PHILADELPHIA AND BALTIMORE-WASHINGTON DERMATOLOGICAL SOCIETIES

Joint Meeting, Baltimore, Dec. 7, 1928

L. W. KETRON, M.D., *Presiding*

LUPUS ANNULARIS OR SARCOID. Presented by DR. KETRON.

An American housewife, aged 60, presented about thirty lesions limited to the face, forehead and ears, which varied in size from that of a pea to that of a quarter. The smallest ones were yellowish, smooth, nonelevated, roundish, irregular implantations in the skin. As they increased in size central clearing took place with thin, soft scar formation and the development of discrete or confluent annular lesions with a yellowish edge, 2 or 3 mm. wide, which was either continuous or formed segments and was usually scaly. Under glass pressure, the infiltration had a lupoid, translucent color. The general physical examination gave negative results.

The Pirquet skin test with Koch's old tuberculin and the Wassermann reaction were negative; roentgen examination of the chest, chemical analysis of the blood, blood cell count and urinalysis were unimportant. In one portion of the section taken for examination, the microscopic changes consisted of a typical diffuse lupus-like infiltration with numerous giant cells but no areas of necrosis. In another portion, there were numerous bundles of sharply defined epithelioid cells, with some nests of lymphocytes which resembled the picture of sarcoid. A few sections stained for tubercle bacilli were negative, but sufficient tissue could not be obtained for inoculation into animals.

The duration of the lesions was four years. The evolution had been slow, and new lesions had gradually appeared. There were no important subjective symptoms.

The patient had always been strong, well nourished and healthy. One child had scrofuloderma.

Thirty injections of gold sodium thiosulphate caused no improvements.

Should this case be classified with the sarcoids or with lupus? A similar case was reported by O'Donovan in the *Transactions of the Dermatological Section of the Royal Society of Medicine* for May 17, 1928, and opinion was divided as to whether the condition was sarcoid or lupus.

DISCUSSION

DR. FRASER: I did not have the opportunity to study the slides from this case, and it is difficult and often impossible to make a histologic diagnosis from a photograph. Some parts of the picture suggested lupus vulgaris and others sarcoid. What is sarcoid? Is it a variety of tuberculosis due to the presence in the tissues of an attenuated form of the tubercle bacillus? The mildness of the reaction would suggest this concept.

DR. SCHAMBERG: I should regard this condition as an annulopapular sarcoid, which is closely similar to that in a case report published from Jadassohn's clinic and also to that in a case under my own observation. The case was that of a woman over 60 years of age, with elevated annulopapular lesions on the face. Indeed, the condition looked like a tertiary syphilid. Under the microscope, the picture was characteristically tuberculoid. The eruption was refractory to a gold compound. Perhaps small doses of neoarsphenamine might be employed in this case with carbon dioxide locally. To be sure, one might employ the designation annulopapular tuberculid, which would perhaps be more expressive of the underlying etiologic condition. It so happens, however, that the term sarcoid has been applied to this special picture.

DR. FOX: As the histologic structure suggests tuberculosis, the possibility should be entertained that this is a case of lupus vulgaris erythematodes (Leloir).

DR. HIGHMAN: In discussing the relative nature of sarcoids and tuberculosis, one constantly loses sight of Boeck's important posthumous report, in which he retracted the term sarcoid and substituted miliary lupoid. In the particular case on which this article was based, tubercle bacilli were found in the lesions. Thus, there can be no differentiation between sarcoid and tuberculosis. In the case presented, the condition looked more like that of disseminated lupus or some other form of tuberculosis than what is called sarcoid, but in view of Boeck's article, it seems desirable to count sarcoid as tuberculosis, too.

GRANULOMA ANNULARE. Presented by DR. PELS.

W. R., a trained nurse, aged 58, single, an American, presented an extensive fibroid infiltration of both lungs (an old tuberculous infection) found by roentgenographic investigation. The lesions on the skin were located as follows: On the right, on the temple, the lower eyelid (disappearance), the axillar near the breast, the shoulder (posterior), the extensor aspect of the thigh above the knee, on the buccal mucosae, the dorsum of the hand, the flexor surface of the forearm (biopsy scar), and on the palm (disappearance); on the left, on the flexor aspect of the wrist, the temple, the dorsum of the hand, the thigh near the groin, the buccal mucosae, the neck, the palm (disappearance), and on the upper and lower lips. The lesions were maculopapular and ranged up to 3 cm. in diameter. They were well defined and had raised, rolled edges and clear centers. Glossy surfaces were present in some lesions. They were lavender striations, but in general the lesions were reddened. Slight infiltration was present. The buccal lesion on the right was round and well defined and had whitish edges.

The Wassermann reaction of the blood was negative. Tuberculin was not given. The biopsy specimen from the right arm showed hyperkeratosis, a thickened stratum granulosum and rete, with obliteration of the pegs. The chief changes were in the corium, occurring as a diffuse infiltration of small mononuclears, an increase in

fibrous tissue cells and some newly formed blood vessels, without special arrangement—a chronic granulation tissue change. The appendages were normal.

The disease began two and one-half years before presentation; it first appeared on the lower right eyelid, then on the hand, other lesions appearing after various intervals. There was a partial spontaneous disappearance of some of the lesions. There were no symptoms (such as itching); the menopause occurred nine years before presentation, and there was no history of the taking of drugs. The patient had typhoid fever eleven years before presentation. Two brothers died of pulmonary tuberculosis.

Roentgen therapy was used with partial success. Various arsenical preparations were taken but not intravenously. Locally, trichloracetic acid, chrysarobin varnish and mercury ointments were used. Phenolphthalein was given by mouth, but caused no eruption or aggravation of the lesions.

The condition was a dermatosis resistant to therapy, with unusual location on the buccal mucosae and on the lips.

DISCUSSION

DR. BECHET: I should like to suggest the diagnosis of lichen planus annularis in this case. The purplish color and the shiny surfaces are strongly suggestive. The borders of the lesions are not sufficiently rolled and waxy for granuloma annulare. There are typical papules of lichen planus on the mucous membrane of the mouth. The clinical evidence, in my opinion, is overwhelmingly in favor of lichen planus.

DR. FRASER: I do not recall having seen this patient, but my impression gained from a cursory glance at the slide was that the histologic picture did not conform with that usually seen in granuloma annulare. For one thing, the cellular infiltration of granuloma annulare is localized chiefly in the deep corium and adjacent subcutis. The infiltration here is located in the upper parts of the corium.

DR. WISE: In view of the location of the lesions and the presence of patches in the mouth, I favor the diagnosis of lichen planus atrophicus.

DR. WEIDMAN: The margins of many of these lesions are beaded, and the first condition that came to my mind was pagetoid epithelioma, but of course the lesions of the mouth are strong obstacles. I finally believe that this is one of those cases of "ringed eruption" which Wende described. On two occasions, Dr. Edward Corson has shown a patient with a condition similar to that of Wende's, and Dr. John Lane was responsible for calling attention to Wende's communication in this connection. Histologic examination in the case is not satisfactory, and I wonder if sections were cut deeper in the block something might not be encountered that would help in making a diagnosis. One jumps at conclusions, or at least forefeits a great deal by not getting all that there is possible to get out of the sections. The older dermatohistologists used to cut serial sections as a routine through the entire block, doing the work themselves. Now, I fear that dermatologists are letting down the bars. They must personally supervise technicians. Often, not enough sections are cut; on the other hand, I do not advocate exhausting and wasting the material when the representative part of the specimen has been satisfactorily examined.

DR. PELS: The diagnosis of lichen planus was considered in this case when the patient was shown once before, and there were certain features in favor of it, as Dr. Bechet has stressed. In addition to these, some lavender striations were present; there was also chronicity, which would be in favor of lichen planus. Certain features, however, made us somewhat unwilling to accept that diagnosis, because of the lack of itching, the unusual location, the general absence of Wickham's striae, the occurrence of the lesions one after another and the rolled edge. Unfortunately, fresh lesions were not seen. The rolled edge would of course favor granuloma annulare. The first lesion, which unfortunately could not be seen when the patient was presented, appeared to be an epithelioma on account of the rolled edge. In fact, it was considered so until the other lesions gradually appeared. After biopsy on the right forearm, the lesions spread; contrary to what recently appeared in the literature regarding the effect of biopsy on other lesions of

granuloma annulare, the lesions did not disappear. The most interesting fact is that lesions occur on the lips and on the buccal mucosae. Consequently, with these facts in mind I have been left in somewhat of an indecision. For the reasons just given, I lean to the diagnosis of granuloma annulare.

A Case for Diagnosis. Presented by Dr. McCarthy.

P. L., an American school girl, aged 7, presented an irregularly rounded area, about the size of a half dollar, on the right cheek. It was pinkish and appeared atrophic. Small pitted scars, about the size of a pinhead, were seen throughout its extent. Three small ulcerations which were covered with adherent crusts were present at the time of examination. No definite infiltration or apple jelly nodules could be made out under a glass depressor. Examination of the chest gave negative results. The tuberculin test was negative locally, but there was perhaps a slight focal reaction. The Wassermann reaction was negative. The mother of the patient refused permission for a biopsy.

The mother insisted that the lesion began as a small "blister," resulting from an injury at the age of 2 years. It has recurred five or six times and had extended with each recurrence. The appearance of a vesicle was preceded by an intense desire to scratch.

DISCUSSION

Dr. Murrell, Dr. Greenbaum and Dr. Eichenlaub thought that this was a case of herpes.

Dr. Hirschler: I suggest the diagnosis of factitious dermatitis.

Dr. Highman: I agree with Dr. Hirschler.

Dr. Klauder: The patient now presents a scar. What lesion produced it is speculation. I should reserve any opinion as to the diagnosis until the patient is seen at the time she presents what the mother describes as a recurrence.

Dr. Smith: I consider this case one of lupus erythematosus.

Dr. Traub: I agree with Dr. Klauder that when one is dealing with a lesion that is only a scar, what the original eruption was must be a guess. The mother says that when the eruption first appeared it became badly infected, and the "pock mark"-like scars would suggest that it had been herpes. The age of the patient and the tvpe of scarring would seem to rule against the diagnosis of lupus erythematosus.

Dr. Bechet: The diagnosis is purely speculative. The eruption might or might not be factitious. The scar is strikingly varioliform; if it were possible for hydroa vacciniforme to recur constantly in the same spot, such a diagnosis might have to be considered.

Dr. McCarthy: The history of the recurrence of a small vesicle occurring practically always in the same location makes one think of recurrent herpes, if the mother's story can be relied on. I, myself, have never seen anything but the scars, horny plugs and crusts. With the exception of Dr. Smith, no one has mentioned the three areas which show real horny plugs deeply inserted in the skin. It is necessary to use a sharp curet to get them out. I have never seen anything like this in a recurrent herpetic lesion. On the other hand, I do not believe, from the appearance of the lesion, that one can say that the condition is lupus erythematosus. The question then arises, how is one to explain these plugs and what can be done to stop the scarring in the patient? Some of the members who have discussed this case have suggested that the child picks her face and that the eruption is self-induced. I cannot agree with this diagnosis.

Tuberculosis Cutis. Presented by Dr. Ginsburg.

B. S., aged 37, a colored housewife, presented an eruption on the forehead, cheeks, eyelids, lips, forearms, fingers, knees, legs and toes. The lesions were crusted, dull red, papulonodules, both discrete and grouped, with the tendency to heal spontaneously, leaving central irregular atrophic and hypertrophic scars.

When the crusts were removed, bleeding points were seen. The skin over the distal portions of the phalanges was involved, resulting in deformity. Three tuberculin tests were negative; the Wassermann reaction of the blood was negative, as was a roentgenogram of the lungs and fingers. No tubercle bacilli were found in the sections. Inoculations into a guinea-pig and pigeon were also negative. Sections from three biopsies showed diffuse lupoid infiltration with giant cells, rare areas of necrosis and strands of epithelioid cells in the deeper cutis. There was little hyperkeratosis and hypertrophy of the epidermis.

The eruption began eight years before presentation on the fingers, and new lesions developed rapidly in the areas named.

There was no change in the appearance of the lesions following two injections of arsphenamine. The case was presented for suggestion as to the proper classification.

TUBERCULOSIS CUTIS OR SARCOID? Presented by DR. A. J. GAGE.

R. W., aged 22, a colored housewife, presented an eruption on the face, neck, bend of the right elbow and around the pubis, with a few papules scattered here and there on the trunk, and a small group on the right buttock. The lesions consisted of roundish or angular, flat, dark red papules or patches, varying in size from that of a pinhead to 2 cm., the largest showing small keratotic plugs. The most numerous ones were grouped over the back of the neck. There were also a few on the eyelids and a large one in the corner of the mouth. The right side of the tongue showed loss of papillae with two eroded papules. The general physical examination gave negative results. Pelvic examination showed some thickening around the ovaries; this had been caused by an old pelvic inflammatory disease not thought to be tuberculosis by gynecologists. There was a slight enlargement of the inguinal, submental and epitrochlear glands. The Wassermann reaction of the blood was negative before and after the injection of 0.6 Gm. of neoarsphenamine. The tuberculin test was negative. Biopsy showed a typical tuberculous picture resembling the usual varieties of tuberculosis more than sarcoid. The lesions began on the back of the neck about one and a half years before presentation and had gradually extended. There was slight itching at times. There had been no previous skin trouble. There were neither genital sores nor a history of tuberculosis. One child was living and well; there had been no miscarriages.

DISCUSSION

DR. KETRON: I hope the members will be good enough to take up the question of the frequent negative tuberculin reaction in tuberculosis cutis of this type.

DR. WEIDMAN: As to the case presented by Dr. Ginsburg, the eruption is indeed extensive, largely on the face but sometimes elsewhere. The interesting point to me was that extensive laboratory tests were made and yet tuberculosis could not be demonstrated. Even the inoculation tests were negative, including those in a pigeon. This looked to me like a case that Dr. Klauder described under the title "Multiple Sarcoid-Like Granulomas of the Skin of Undetermined Nature" (ARCH. DERMAT. & SYPH. **13**:695 [May] 1926). Clinically, his experience was much the same as here. Histologically, both the lesions on the skin and the enlarged lymph nodes had shown tuberculous architecture. When the patient was first shown before the Philadelphia Dermatological Society, many members thought that the condition was syphilis. Tubercle bacilli could never be demonstrated. In short, the condition remained undiagnosed. At necropsy we took pains to take out a large number of lymph nodes, but although all showed tuberculous architecture, none produced tuberculosis when inoculated into guinea-pigs. The lungs, however, contained a large cavity, and material from this produced extensive tuberculosis and death in guinea-pigs. It is evidently possible for what appears to be tuberculosis of the skin to be present and not be capable of giving the laboratory diagnosis of tuberculosis. There may be another reason why there was a failure to reproduce the disease in guinea-pigs; I am thinking of the avian strain, on which Dr. Ginsburg or Dr. Ketron has checked up. My belief is that the condition is tuberculosis.

As to the tuberculin test, I am not an expert. I have a general impression that the tuberculin test, as it is known today, is not all that it ought to be. It has been experimented with and employed as a routine for years, and yet how much does one depend on it? Once in a while the results are striking, but I do not think that, statistically, useful results are obtained often enough. Of course, it is easy to speculate on why this should be. Are antigens being prepared in such a way that they can be adapted to the varying circumstances that obtain in cutaneous tuberculosis? Possibly avian or perhaps fish tuberculosis antigens should be employed on such a place as the skin. The situation is most complicated. Nowadays one talks about mutation in tuberculosis bacilli, even to the extent of filter-passing forms. From the standpoint of preparing particularly appropriate antigens, the problem seems to be interminable.

As to the case presented by Dr. Gage, I believe that it is a case of miliary lupoid of Boeck. The histologic picture did not conform to the classic picture of sarcoid, there being so many giant cells, although I do not insist that there is any precise, sharp differentiating line histologically between what may be clinical sarcoid, on the one hand, or miliary tuberculosis of the skin.

DR. MCCARTHY: In regard to the tuberculin test as a diagnostic agent in tuberculosis of the skin, I had occasion to use the ophthalmic tuberculin test in a large group of cases several years ago. I was much impressed by the absence of reactions in some of the advanced forms of the condition, and pronounced reactions locally in the eyes of the patient with early forms. I believe that patients with advanced cases are so overwhelmed by toxins that they do not react to small local doses of tuberculin. The probable minute dosage of tubercle bacilli in these tuberculous lesions of the skin may be the factor, and the patient, not being sensitized to the tubercle bacillus, will not react to small antigenic doses. The real answer to the question of the reaction to tuberculin in these cases has still to be worked out.

DR. FRASER: The case reported by Dr. Ginsburg is probably tuberculosis. I should be inclined to classify the case reported by Dr. Gage as an example of Boeck's multiple benign sarcoid. The lesions on the neck bear a strong clinical resemblance to the papules of lichen planus. Dr. MacKee presented an almost identical case at a recent meeting of the New York Dermatological Society. Histologically, MacKee's case was sarcoid.

Replying to Dr. Ketron's question in regard to the difference between the giant cells of tuberculosis and those of sarcoid, in the cases of sarcoid that I have observed, the process appeared to be the expression of a milder reaction than that found in lupus vulgaris. The giant cells of sarcoid showed a greater variety of form, and their cytoplasm did not have the hyalinized appearance that is characteristic of the giant cell in ordinary tuberculosis. The cytoplasm of the sarcoid giant cell presents a "foamy" surface similar to that described by MacCallum as characteristic of the giant cells of lepra. I know that I may be criticized for this view, but I have observed these features in a number of cases.

ACNE NECROTICA. Presented by DR. KETRON.

G. F. K., a white man, aged 53, a clerk, on Nov. 5, 1928, presented an eruption which involved the entire scalp, particularly the top, which was bald, and the nose. The lesions consisted of papules or pustules the size of a pinhead, some of which showed crusts, underneath which there were small punched-out ulcers. There were also numerous slightly depressed, roundish or irregular scars. The nose showed marked scarring and was a dark red. General physical examination gave essentially negative results. The teeth were bad, and the tonsils had been removed. The Wassermann reaction was negative. The intracutaneous tuberculin test with 0.1 mg. was positive. Cultures from pustules on the scalp showed a white staphylococcus and acne bacilli. The latter was the predominating organism. The roentgenogram of the teeth showed six which were extensively infected and some others more or less involved. Intradermal skin tests with a

whole killed broth culture of the staphylococcus obtained from the scalp gave no allergic reaction. The disease started on the nose on Jan. 1, 1928, following a burn from a Roman candle. Pustules developed on the nose, later extending on to the scalp. The condition had improved at times under local treatment but had never entirely healed. About two weeks before presentation, the patient developed a large furuncle on the arm and one on the neck. The staphylococcus obtained from these lesions was not the same as the one obtained from the pustules on the scalp. Infected teeth were removed on Nov. 8, 1928, and the patient was given metaphen solution for local use. After about one week the lesions had practically healed and had remained so until the time of presentation.

The interesting feature about this case was the wide distribution of the lesions on the scalp and the rapid disappearance of them after the removal of the infected teeth. It is realized, however, that this does not necessarily mean that the healing was due to the removal of the teeth, as the condition had cleared up almost as much on previous occasions. (The condition relapsed one week after the patient was presented to the conference.)

DISCUSSION

DR. MCCARTHY: I noticed that the tuberculin reaction was positive in this case. At the present time in Europe many authorities look on acne necrotica as possibly of tuberculous origin. In a great many cases in addition to the superficial ulcer, microscopic examination shows small areas of coagulation necrosis surrounded by large numbers of epithelioid cells and a sprinkling of small lymphocytes. This is the picture often seen in lesions that are now known to be true papulonecrotic tuberculids. Again, from the clinical point of view, these lesions often heal with scars similar to those of true tuberculids. I believe that eventually it will be agreed that acne necrotica should be classified as a tuberculid.

DR. WEIDMAN: I am sure that most dermatologists have long considered these cases as tuberculous. But, as I recall it, a great deal of work was done four or five years ago at the Skin and Cancer Hospital in New York and the conclusion was reached that these cases were due to ordinary bacteria — not the tubercle bacillus.

DR. KETRON: In the past two or three weeks this patient has developed two large furuncles, one on the neck and one on the arm. I was interested to learn whether the staphylococcus causing the boils was the same as that which had been obtained on culture from the lesions of acne necrotica. The organisms, however, were entirely different, the one from the furuncles being *Staphylococcus aureus*, while that from the scalp was of the white variety. As noted in the history, cultures from the lesions on the scalp showed acne bacilli and white staphylococci, the former being by far the predominating organism. Whether or not the acne bacillus had anything to do with the development of the lesions is rather doubtful. I am convinced, however, that this organism, although it may not be actively an infecting agent, may be responsible for local change due entirely to its action as a foreign protein. Some other agent may cause a break in the follicular sheath, thereby allowing the acne organism to exert its influence on the unprotected tissues. Intradermal injections of the organism into rabbits will cause abscesses, which may persist for several months.

PRURIGO NODULARIS. Presented by DR. GOODMAN.

K. A., an American woman, aged 50, single, a clerk, presented an eruption which consisted of papulonodular lesions, thickly scattered over the hands and arms, less so on the feet, legs and buttocks. They ranged from 2 mm. to 1 cm. in diameter; they were hard and infiltrated, and varied from pink to grayish red, hardly differing from the normal color of the skin. Most of them had a central depression, a small central dry scale or crust, and round and linear excoriations. Each lesion was originally topped by a vesicle. The results of the general physical, neurologic and gynecologic examinations were negative. Gastric analysis revealed achylia. Roentgen examination of the gastro-intestinal tract showed spastic

irritability. The Wassermann reaction of the blood was negative. Skin tests made with cutaneous grains, epidermal extracts, dairy products, fish and pollens were all negative. The basal metabolic rate was minus 27. Several biopsies were made, and special study of the nerve fibers revealed no abnormal changes. No particular localization of inflammatory infiltrate was noted around the nerve fibers (Bielschowsky's stain). The condition began six years before presentation as "hives," which disappeared and recurred. The patient had been nervous since childhood, more so since the onset of the eruption. She had had indigestion, constipation and painful menstruation the last of which she considered provocative of the eruption. Tonsillectomy and drainage of the sinuses were performed eleven years before presentation. Itching had always been severe. Treatment consisted in intensive local, chemical and roentgen therapy, glandular extracts (thyroid, ovarian) and a compound solution of iodine. There was no improvement in the eruption.

There have been atypical recurrences at the sites of biopsy. The possible neurogenic origin of the eruption was not conclusive from microscopic study. Primary degeneration of the cutaneous nerves was not established.

DISCUSSION

DR. HAZEN: This patient has lesions on both the legs and the arms. A patient of mine had exactly the same type of lesions, but only on the legs. A rather interesting feature was that a number of them cleared up spontaneously. The histology agreed with that already described in various cases of prurigo nodularis. It was interesting to note that no invasion could be detected along the nerve trunks. I wish that I could say something about the causation of this disease, but to me it is still one of the mysteries. Treatment is just as hopeless, for the lesions have a way of recurring, even after excellent operative intervention.

DR. KETRON: This case was also presented at the American Dermatological Association at its Baltimore meeting in 1927. I remember at that time that Dr. Pautrier said he believed that itching is the primary factor in this disease and that the lesions develop secondarily due to scratching. It is difficult for me to believe, however, that these nodules are purely a tissue response to trauma. The remarkable feature about this case is the extreme refractoriness of the lesions to any kind of therapy. Some of them have become desiccated and have returned. One or two others were given 2 units of the roentgen rays without any effect.

DR. RULISON: I noticed that all three scars made by the biopsies showed marked keloidal tendency. Is it possible that this tendency has any relation to the development of the nodules?

DR. STOKES: The point is well taken. I recall a case at the Mayo Clinic which is practically a duplicate of the one presented, though it lacked one feature, that is, itching. The patient was under observation for some time. These lesions all began with follicular pustules which on involution left a gradually developing hard nodule almost identical with that of the patient presented, with a slight central necrosis at the point at which the pustule had developed. She was under observation at intervals for more than two years. Apparently she was suffering from some homologue of dermatitis papillaris capillitii or acne keloid on her arms. I think that the patient presented has a pruritic process on a neuropathic background. The nodules, rather than the conventional conception of primary prurigo nodularis, may be secondary.

DR. SCHAMBERG: Several years ago, Dr. Hirschler and I published reports of two cases of this condition under the term "multiple tumors of the skin associated with itching." Dr. Hirschler excised one of the lesions and found that it returned in situ, not, however, in the form of keloid. This subject has been discussed in many papers, and certain authors have been more inclined to give it the name of lichen obtusus corneus, indicating that it really belongs in the group of lichens. I am inclined to the view that the condition starts primarily as pruritus and that the growths in the skin represent a peculiar tissue reaction.

Concerning treatment, one of my patients with scores of lesions over the body observed the complete disappearance after the use of thyroid extract and baths with hot magnesium sulphate, but this method of treatment failed in two other cases.

DR. HAZEN: I do not think that the lesions are keloidal growths for two reasons. First, nothing suggests keloid histologically, and second, the lesions did not respond to the roentgen rays the way keloid growths usually do.

DR. KLAUDER: Most of the patients with prurigo nodularis are neurotic, which probably supports the contention that the malady begins as pruritus. I should place this disease in the group of cutaneous neuroses. Considerable time should be spent in taking a history of these patients to elicit a psychogenic factor. Therapy should be directed at the underlying nervous condition of the patient rather than mere treatment for the nodular lesions.

POLYCYTHEMIA WITH DERMATOSIS. Presented by DR. EICHENLAUB.

J. J. O., aged 48, an American, a carpenter, was given a complete examination by Dr. John Minor, his physician, which showed the following abnormal manifestations, aside from the condition of the skin: The spleen was enlarged and easily palpable. There was inguinal adenopathy only. When first seen, the fully developed eruption presented a universal, scaly, dark purplish-red, itchy erythrodermia, with swelling of the hands, feet and ankles due chiefly to congestion and to some edema. At the time of presentation, the same picture was present, with the exception of the purplish color, which was probably due to polycythemia. The urine contained a few granular and hyaline casts. The blood counts are shown in the accompanying table. The Wassermann reaction was negative on several

Blood Counts for J. J. O.

Date	Test	Hemoglobin, Per Cent	Red Blood Cells	White Blood Cells
May 26, 1926	Dare	115-120	8,760,000	19,450
May 30, 1926	Dare	110 plus	8,700,000	19,800
June 8, 1926	Dare	110	8,570,000	.....
June 10, 1926	Dare	115	8,200,000	.....
June 12, 1926	Dare	110	8,200,000	21,100
June 14, 1926	Dare	110	8,150,000	17,200
June 16, 1926	Dare	105	8,000,000	21,250
June 18, 1926	Dare	105	7,900,000	20,250
June 21, 1926	Dare	110	7,650,000	21,550
June 23, 1926	Dare	105	7,540,000	25,350
June 25, 1926	Dare	105-8	7,000,000	19,550
June 28, 1926	Dare	108	6,900,000	20,300
June 30, 1926	Dare	105	6,500,000	15,800
July 2, 1926	Dare	100	6,500,000	17,850
July 6, 1926	Dare	95-100	6,400,000	17,300
July 9, 1926	Dare	95	5,700,000	16,650
July 12, 1926	Dare	95-100	5,400,000	16,150
July 16, 1926	Dare	95-8	5,500,000	14,650
July 20, 1926	Dare	95	5,500,000	13,900
July 26, 1926	Dare	95	5,900,000	9,900
Aug. 4, 1926	Sahli	95-100	5,200,000	9,450
Aug. 11, 1926	Sahli	95	5,400,000	8,450
Aug. 18, 1926	Sahli	90-95	5,000,000	8,550
Aug. 25, 1926	Sahli	90-95	4,800,000	10,550
Sept. 17, 1926	Sahli	85 plus	4,970,000	11,700
Sept. 24, 1926	Sahli	85 plus	5,100,000	9,800
Oct. 1, 1926	Sahli	85	4,940,000	9,100
Oct. 10, 1926	Sahli	75	4,850,000	8,450
Oct. 20, 1926	Sahli	75-80	4,660,000	11,500
Nov. 5, 1926	Sahli	85	4,440,000	5,500
Nov. 16, 1926	Sahli	85	4,280,000	7,200
Dec. 8, 1926	Sahli	85	5,000,000	8,100

June 18: Polymorphonuclears, 80.8; eosinophils, 1.6; basophils, 1.6; small mononuclears, 13.6; lymphocytes, 2.4.
July 11, 1928: Temperature, 98.8 F.; weight, 178¾ pounds (81 Kg.).
July: Hemoglobin, 70 per cent; red blood cells, 3,930,000; white blood cells, 6,400.
May 25, 1927: Wassermann reaction, negative.
Dec. 8: Polymorphonuclears, 64 per cent; small mononuclears, 34; eosinophils, 2.

occasions. The biopsy specimen (taken during the second attack, when the blood count showed anemia and not polycythemia) was presented with the patient. It showed chiefly acanthosis, edema of the papillae and throughout the dilated lymph spaces and a diffuse infiltration most marked in the papillary layer and around the blood vessels.

About December, 1926, the patient noticed itching and an eruption on the ankles. This gradually developed into a general eruption with intense itching.

Phenylhydrazine hydrochloride, 1 Gm. a day, was taken by mouth. For the condition of the skin, roentgen therapy, ⅛ unit once a week, was given over the whole body, one third of the body being treated at one sitting. Under this treatment the eruption cleared up entirely but relapsed after three months to the condition presented. The polycythemia did not return.

DISCUSSION

DR. HIGHMAN: A patient with probable polycythemia, who was under my care, had lichenification and dermatitis of the neck and face for several years preceding the general disturbance.

DR. WEIDMAN: Why was phenylhydrazine hydrochloride selected for use in treatment?

DR. SCHAMBERG: If one is looking for a drug to destroy red blood cells, one can readily find it in lead. One hundred milligrams of lead in the form of a colloidal lead or in certain other preparations virtually destroys one half of the red blood cells. Perhaps in polycythemia, the use of small doses of lead might accomplish the result desired.

DR. EICHENLAUB: In this case, the diagnosis of polycythemia was made by a competent internist. The patient had inguinal adenitis and a markedly enlarged spleen. When he was first seen, the lips were ruby-red and the skin a distinct purplish color, symptoms which accompany polycythemia. The blood count was so consistently high that there seemed to be no question about this condition being polycythemia vera. Polycythemia may occur symptomatically as the result of a person going into high altitudes, as a secondary condition to hypertension, nephritis, diabetes and to congenital heart disease. I looked up the literature back to the time of Dr. Osler's description in 1903. From the titles of the articles, nothing similar to this case has appeared in the literature. One case of acne rosacea was reported by a French author, but no other case similar to this. I also noticed in the literature that there were a number of patients with polycythemia vera who subsequently died of leukemia. There may be some association between leukemia and polycythemia. With the present relapse in the presence of anemia of the patient reported it seems possible to me that he may ultimately disclose a leukemia.

NEURODERMATITIS OR LICHEN PLANUS. Presented by DR. GINSBURG.

M. E., aged 49, married, a housewife, presented an eruption in the region of the left knee which consisted of raised, flesh-colored, pinkish keloidal-like nodules, averaging 3 mm. in diameter; they were discrete but for the most part confluent, and arranged in lines running transversely across the skin. Section showed hyperkeratosis, acanthosis and a slight amount of spongiosis; the rete pegs were thin and elongated. The elastic tissue in the papillary and subpapillary layers had practically disappeared. In the cutis, there was a proliferation of connective tissue and a formation of new capillaries. A few round cells were present, mostly around the blood vessels. The eruption had been present for ten years, and at times was associated with severe itching. The patient was presented on account of the peculiar arrangement of the lesions.

DISCUSSION

Every one agreed on the diagnosis of neurodermite.

A Case for Diagnosis. Presented by Dr. Eichenlaub.

L. P., aged 31, an American, a war veteran, presented a solid, dark red, scaly, lichenified and in places superficially ulcerated eruption on the left leg only, with a few new isolated papular lesions at the upper edge. There was a mass of enlarged lymph glands in the corresponding inguinal region, which were hard and not matted together. The general examination gave negative results. The Wassermann and Kahn reactions were negative. The urine showed a trace of albumin. The blood count showed: red blood cells, 4,656,000; white blood cells, 14,850; differential: polymorphonuclears, 71 per cent; small mononuclears, 22 per cent; large mononuclears, 50 per cent; transitionals, 1.5 per cent, and eosinophils, 0.5 per cent. The chemical analysis of the blood showed: nonprotein nitrogen, 39.8 mg., uric acid, 1.9 mg. and sugar, 95 mg. per hundred cubic centimeters. Cultures from a lymph gland were negative. Cultures from the lesions of the skin revealed *Streptococcus viridans* and *Streptococcus hemolyticus.* No fungi were demonstrated directly or by culture. A biopsy of the skin showed chiefly hyperkeratosis, acanthosis, hyaline degeneration of the connective tissue and a marked infiltration throughout the section with lymphocytes and plasma cells; only one giant cell was noted. Section of a lymph gland revealed a diffuse nonspecific inflammatory infiltrate.

In 1918, the patient scratched the ankle on a saddle buckle, and the condition gradually spread constantly until the condition present on examination developed.

DISCUSSION

Dr. Klauder: Is this a compensation case?

Dr. Eichenlaub: The condition developed while the patient was in the army, and the question of a self-induced eruption was considered, but it was felt after due consideration that this impression was not warranted.

Dr. Wise: I suggest the diagnosis of dermatitis vegetans, a disease of unknown etiology and one lacking a definite microscopic picture. I do not believe that malingering played a rôle in the cause of the disease.

Dr. McCarthy: I wonder whether or not *Streptococcus viridans* found in cultures of the lesion is a factor in this case. This organism, present in its usual habitat, the oral cavity, and in secondary endocardial and joint involvement, is not often found in skin lesions. How many observers have noted this particular organism as a primary offender or as a secondary contaminating factor in dermatologic cases?

Dr. Brown: *Streptococcus viridans* is normally present in the mouth. *Streptococcus viridans* is the name of a large group of streptococci. It is by no means certain that many of them are pathogenic. Certainly most of them are not pathogenic when found in the mouth. It is not at all surprising that they should be found in any superficial lesions of the skin and that they should grow there, because the presence of serum greatly favors their growth. They also are able to grow as contaminating or secondary invaders.

Dr. Schamberg: In our institute some observations have been carried out in which it is shown that streptococci are commonly present on the normal skin. They are found not merely under the nails but not infrequently on the arms. If one scrapes the skin and takes cultures on Rosenow's brain medium, one will be surprised how often streptococci can be found on a skin that shows no change.

Dr. Whitehouse: I agree with Dr. Klauder's interpretation in this case. While the patient is not the usual nervous type seen in these cases, it has been a compensation case of long standing, and it is of distinct advantage to him to be thus affected. I should apply Unna's gelatin-zinc-lime paste with gauze bandaging, removing it every few days; the moisture will soon diminish, and the infection will stop in a short time.

Dr. Klauder: I had in mind two conditions when I asked if the case was a compensation one: first, the possibility of malingering and second, the possibility

of a psychogenic influence in the causation and continuation of the lesions, somewhat comparable to the mechanism of the formation of a blister under a postage stamp when a hypnotized person is told that a cantharides plaster is placed on the skin and that a blister will be produced. Again, the variable cutaneous lesions in hysteria should be considered. If the patient is being benefited by the continuation of the lesion, this fact, that of a psychic fixation, suggestion, should be considered in the etiology of the lesion.

DR. FRASER: The histologic picture in the lymph node fits in with the theory of infection. The picture is that of hyperplastic lymphadenitis and closely resembles the lymphadenitis that has been observed in primary exfoliative dermatitis.

DR. BLAISDELL: In conditions in which a sealed dressing is desirable but impossible, the same end can be reached by strapping the ordinary dressing with adhesive plaster which is crisscrossed with pen marks. It is impossible for a patient to remove the adhesive strapping without detection.

DR. EICHENLAUB: In the first place, the observations from the laboratory were recorded as they were received. I, myself, would not consider the streptococcus to be the etiologic factor. The patient has been in the hospital more than a month, and has had his leg dressed twice daily by a physician. So far, there has been no evidence that the patient has tampered with the dressing. I do not think that he could have manipulated it enough to produce the picture seen today without detection, as we have had a self-induced eruption in mind. We shall endeavor to rule this question out and report on it subsequently.

[NOTE: Since the patient was presented, a fixed dressing has been applied that was so marked that it could not be disturbed without the knowledge of the attending physician and was changed only by the physician for a period of three weeks, without any effect on the appearance of the lesion.]

MELANOMA. Presented by DR. GATELY.

C. J. H., aged 25, an American shipping clerk, presented an area on the forehead the size of a dollar, which extended into the hairy scalp, and was made up of irregularly shaped nodules forming a mass covered by slate-colored skin. The Wassermann reaction was negative and the blood picture, normal. The lesion was present at birth as a flat, pigmented spot. Nodules appeared first seven years before presentation. The lesion had not increased in size during the past year. There was no history of malignant disease in the family. The case was presented for suggestions as to treatment.

DISCUSSION

DR. BECHET: The case presented is a classic example of the disease. The most important point is in reference to treatment, as these cases frequently terminate fatally no matter what treatment has been instituted. The case recalls to my mind a dramatic experience a few years previously: A man came to the clinic for the relief of a melanotic growth on the tongue, which exactly resembled the one under discussion. There were no apparent metastases, and the patient was robust and well set up and said that his general health was perfect. A week or so later, the tongue was excised by a surgeon, and on section the growth was found to be a melanosarcoma. In spite of extensive resection of the lymph nodes, metastasis quickly followed the operation, and the patient died within three months. It seems to me that there are two alternatives in this particular case, either to leave the growth severely alone or to do as radical an operation as possible, preferably through endothermy.

DR. MCCARTHY: This case is presented with the diagnosis of melanoma. It is important to decide what type of melanoma is being dealt with here. Its peculiar blue color and its location near the midline of the forehead classify it as a blue nevus of Jadassohn. I saw this patient just a year ago at the local dermatologic society, and I believe that the lesion is more elevated and has more of a nodular

character at the present time. It is also possible that it has increased about 0.5 cm. in extent. These tumors are composed of melanoblasts of connective tissue origin, and it is characteristic of them that in the beginning they develop in the center of the lesion, forming nodules that lift up the skin rather than by the process of peripheral extension, as in the case of degeneration of the ordinary pigmented mole. The degeneration of the blue nevus is excessively rapid with the formation of early metastases, and I should recommend that this lesion be destroyed by coagulation over a wide area beyond the actual tumor and that healing be assisted by skin grafting. Of course, it is evident that such a process is useless if metastases have already been formed.

DR. ELLER: I should be inclined not to treat this nevus at the present time. As it has not grown in a year, I think it safer to leave it alone than to treat it. Even with the use of the most radical surgical intervention indicated here, such as extremely wide excision circling the apparently normal skin for 2 inches (5 cm.) or more away from the visible part of the lesion and cutting down as deeply as possible and into the fatty tissue, removing this tissue with the lesion without disturbing it, the prognosis would still be uncertain, for it is impossible to know in advance how far from the visible part of the lesion the pigment-bearing cells might be. These pigment-bearing cells at times infiltrate the tissue microscopically as much as 4 or 5 inches (10.16 or 12.7 cm.) away from the projecting black mole. In our clinic we do not make a practice of removing melanomas unless they are subject to traumatism or when they have been traumatized and have started growing. We remove them by means of the endotherm knife in the following way: If the lesion is the size of a pea, for example, we use the endotherm knife to make a circular cut, having a diameter of about 4 inches, going down to the fat perhaps ½ inch (1.27 cm.) or more and removing this entire tissue without disturbing the lesion, if possible. With this radical removal our pathologist, Dr. Satenstein, has been able to demonstrate in some cases the pigment-bearing cells in the lower part of the fat and several inches away from the lesion. This infiltration of pigment-bearing cells is a possibility, but some of these black moles are encapsulated and in these cases radical removal is done; the prognosis is good. Another point is that radium is poor treatment for melanomas, as pigment does not respond to radium unless ulcerating doses are given.

DR. STOKES: I have witnessed the efforts made to remove tumors from this particular part of the skull. The surgical problem is not at all simple and should not be handled by a tyro. If the lesion is to be removed, it should first be thoroughly coagulated, and the work should not be done with a knife. Following the coagulation a surgeon accustomed to operating on the brain should carry through the proper preparation of the field either for graft or for spontaneous epithelialization, if necessary by promoting the growth of granulations through perforations in the outer table of the skull. This is work for the expert or at least one familiar with plastic restoration on the scalp.

DR. TRAUB: The method of local treatment in these cases, I think, is fairly definitely settled, radiotherapy and ordinary surgical intervention with the knife being displaced in favor of the cautery, endotherm knife or electric coagulation. I believe the great mistake that is made in most cases is that the patient is not thoroughly examined for possible metastases before any kind of local treatment is attempted. Should a general physical or roentgen examination reveal metastases, the local lesion should be left alone. When the local lesion is small and is not increasing, it is questionable whether or not it should be removed. But if it is increasing in size, immediate and wide removal is indicated with possible inclusion of nodes of local drainage.

DR. STOKES: It is a well taken point made by Dr. Traub that a patient should have a careful examination for metastases before anything is attempted in dealing with the individual lesion. This should include a roentgenogram of the lungs. I should like to direct attention, too, to the bad practice of feeling, handling and malling these lesions about in the process of examination.

DR. KLAUDER: Dawson, who carried out extensive studies on the melanomas, emphasizes that malignant melanomas always arise from a nevus cell tumor. If this is the blue nevus of Jadassohn, I understand that such a lesion does not contain the nevus cell.

BLASTOMYCOSIS? Presented by DR. ROSENTHAL.

M. T. H., an American, a farmer, aged 72, presented an eruption on the face, neck and right wrist. A typical lesion (on the right side of the face) was well defined and circular, the size of a half dollar, verrucoid, elevated, and bled easily on irritation. The edges were sloping, violaceous and revealed abscesses the size of a pinhead and larger. There was no marked infiltration. On the left cheek and behind the right ear, the skin was a dull violaceous color and was covered with keratotic plaques. General examination revealed arteriosclerosis (blood pressure, 150 systolic and 84 diastolic), conjunctivitis, blepharitis, dental caries and a few enlarged glands in the neck. A roentgen examination of the chest showed bilateral pulmonary fibrosis, dense hilum shadows and an enlarged aorta. The Wassermann (Kolmer) reaction of the blood was negative. Fresh specimens of pus were examined and showed suggestive double-contoured bodies. The onset occurred one year before presentation following a deep cut from a razor on the right cheek. The wound became infected, and began to spread about two months later. There was some itching and slight pain, followed by healing and fresh outbreaks. All the lesions except that on the right cheek improved after increasing doses of iodides and wet antiseptic dressings. There was difficulty in demonstrating blastomyces in the fresh specimen. Several cultures produced a staphylococcus and once *Streptococcus hemolyticus*.

DISCUSSION

DR. GOODMAN: I saw some fresh specimens of pus from the lesions, especially from the one on the face. I was almost convinced at the time that I saw what appeared to be double-contoured organisms, but I could not follow up this observation successfully with specimens which I obtained myself. Just before the meeting, I received slides of the biopsy specimen from the lesion on the wrist. I could not find morphologic evidence of blastomycosis. There were no double-contoured bodies and no typical intra-epidermal abscesses with the marked acanthosis which is usually seen in blastomycosis. From the microscopic standpoint, the process strongly suggests to me a tuberculous change.

DR. SMITH: The lesions on the right side of the face and on the back of the left hand are fairly characteristic of blastomycosis. These are elevated, fungating lesions with small pustular points. The diagnosis will depend on finding the organisms. It is known, of course, that the yeast cells are not always easily found. The entire contents of one of the small abscesses in the border of the lesion should be placed on a glass slide and examined for the double-contoured cells.

DR. STOKES: I am perhaps the only middle westerner here, and I am not going to let this condition pass without protest as a clinical blastomycosis. Perhaps in the East, under the benign influence of the climate, blastomycosis takes unique forms. By the standards of the West, however, this is certainly not blastomycosis, unless I am mistaken. Speaking in dermatologic slang, the process looks not unlike an acrodermatitis of Hallopeau plus a dermatitis repens with a single pyogenic vegetative lesion in the scar, which of course may be epitheliomatous. Pagetoid pre-epithelioma on the face sometimes presents this picture, but obvious pyogenic elements elsewhere and the absence of the typical morphology of blastomycosis certainly require more than clinical grounds for the diagnosis that has been offered.

DR. SCHAMBERG: I agree with Dr. Stokes concerning the diagnosis. I have not seen any cases of blastomycosis in the East which were in harmony with the picture presented by this patient. The eruption on the hands is distinctly a pyogenic infection with undermining of the epidermis. The vegetating lesion on the face might well be an epithelioma.

DR. WEIDMAN: I noticed the soft character of the scar at the back of the neck. I have never seen a scar of that sort in any condition but syphilis. Has the Wassermann test been performed on the blood more than once?

DR. GOODMAN: The biopsy specimen was obtained from the right wrist. As a matter of fact, we were doubtful all along about the case. After I saw the specimen on the slide, I felt that the condition simulated tuberculosis more than anything else, in view of the fact that there were typical giant cell tubercles with the usual chronic inflammatory infiltrate, particularly in association with the vessels. This diagnosis seems to me most appropriate in view of the negative Wassermann reaction and the fact that efforts to demonstrate blastomycetes from what appeared to be intra-epidermal abscesses proved repeatedly fruitless. Inoculations into guinea-pigs will, of course, be made.

ULCER OF THE LEG WITH UNUSUAL BACTERIOLOGY. Presented by DR. KETRON.

F. P., aged 22, an American, a worker in a tin mill, came to the clinic on Nov. 10, 1928, with an ulcer just below the calf of the right leg, which measured 3 by 5 cm.; the edge was indurated, irregular and slightly undermined. It was 3 or 4 mm. deep, and the base was covered with a foul-smelling, thin, bloody pus. Bleeding was easily induced. The general physical examination gave negative results, with the exception of mitral insufficiency following a rheumatic attack four years before presentation. The Wassermann reaction of the blood was negative. Cultures showed, in almost pure form, a gram-negative, short, nonmotile, encapsulated bacillus, which was identified by Dr. J. Howard Brown as *Bacillus ozenae* of Abel. The patient's serum did not agglutinate the organism at first, but after ten daily injections of a vaccine, agglutination took place in a dilution of 1 : 320. Microscopic observations of a section through the edge of the ulcer showed an extremely vascular granulation tissue with chronic inflammation. Bacterial stains revealed a few micro-organisms in the edge of the ulcer, which were thought to be the bacillus described. A small amount of pus from the ulcer and a broth culture of the bacillus failed to produce any lesion after being rubbed into a scarified area on the patient's leg. The ulcer had been present for nine months following a puncture wound with a piece of tin. Two weeks after the patient came to the clinic, another lesion appeared just above the ankle on the same leg. It reached the size of a large bean, and cultures showed the same bacillus as was found in the large ulcer. For the first three weeks various antiseptic dressings were employed, with slight improvement. After ten daily injections of an autogenous vaccine of *Bacillus ozenae*, however, improvement took place rapidly and at the time of presentation both ulcers had almost healed over.

It is believed that *Bacillus ozenae* is probably the cause of the ulceration, since it was the predominating organism and because the ulcer was unusual in appearance, not the kind usually due to the common pyocci.

DISCUSSION

DR. BROWN: This was my first acquaintance with this particular organism. Repeated cultures showed the presence of an encapsulated gram-negative bacillus in large numbers. Occasionally, a few gram-positive cocci were also found but not constantly or in sufficient numbers to indicate that they were the etiologic agent. The bacillus found is not commonly found on the skin. Culturally, it corresponds to *Bacillus ozenae* of Abel (1893) and is not to be confused with a different organism of similar name described by Perez (1899). It is necessary to bear in mind that two organisms of this name have been described. The organism of Perez is probably the better known. The organism isolated from this patient produces a foul-smelling abundant growth on agar or in broth. When injected subcutaneously into a mouse, it produced an ulcer which, however, was of short duration. A guinea-pig into which intraperitoneal injections were made died of peritonitis. A guinea-pig and a rabbit into which subcutaneous injections were made developed local abscesses which persisted for two weeks or longer but disappeared without discharging. When reinoculated intracutaneously into the

patient from whom it had been isolated the culture did not produce a lesion. The serum of the patient showed no agglutinins for the organism. After the administration of ten injections of a vaccine made from the organism, the patient's serum had an agglutinin titer of 1:320. The vaccine treatment was accompanied by marked improvement in the ulcer. The fact that this organism is not a common skin contaminant, that it was found in large numbers and almost pure culture in the ulcers and the response to vaccine therapy led us to believe that this organism, if not the primary cause of the ulcer, was at least responsible for its continuance.

DR. KETRON: Will Dr. Brown please describe the way in which he administered the vaccine?

DR. BROWN: Some experiments reported before the Society of American Bacteriologists and carried out with red blood cells, bacterial vaccines and other antigens indicated that the quickest immunity response was obtained by giving ten daily injections and then waiting nine days to draw the sample of blood for titration. The patient under discussion was given six daily subcutaneous injections of vaccine; he was allowed to rest for nine days and was then given four more daily injections.

DR. MCCARTHY: The use of an autogenous vaccine in this case confirms my results in cases of ozena in which I have used autogenous vaccines with prompt improvement in the condition. Was there any difference in the character of the growth on culture mediums, in this case, from that found in the other organisms in the *Bacillus mucosus capsulatus* group?

DR. BROWN: It was very similar.

KERATOSIS PILARIS OF UNUSUAL TYPE ASSOCIATED WITH DYSPITUITARISM. Presented by DR. PELS.

S. G., aged 11½, a Jewish school boy, presented changes in the skin which were located on the eyebrows, cheeks and upper part of the arms. The skin had a nutmeg-grater appearance with numerous tiny, shiny papules which were grouped and confluent, and showed mild scaling. The lesions on the face bore no definite relationship to the hair follicles. There was a noticeable deficiency of the eyebrows. There was a partially descended testis on the left, and a systolic murmur was present over the pulmonary area (patent ductus arteriosus?). There was a deficiency and an absence of hairy growth, and the clammy hands, acrocyanosis and female stature pointed to an endocrinopathy, probably hypopituitarism.

Stereoscopic roentgenograms revealed a normal sella turcica. A Wassermann test of the blood was declined, but a sugar tolerance test (80 Gm. of dextrose) gave a highest reading of 0.102 per cent. The basal metabolic rate was plus 1. Biopsy was refused.

The patient had one sister who was normal. The father was said to have a loss of hair on the body. The patient's disease had been present since birth. It began on the eyebrows as "red dots" and gradually became worse. For the past seven years, the eyebrows had been growing. No hair was seen on the body. The child was nervous and a "mouth breather."

Various ointments (sulphur, acid salicylic and mercury) were used; roentgen therapy (erythema dose) was given on the eyebrows and cheeks. Compound solution of iodine, solution of pituitary, and a mixed gland preparation and a low caloric diet were prescribed without appreciable effects. The patient was shown for suggestions as to therapy.

DISCUSSION

DR. HIGHMAN: I think that this case is one of ulerytherma ophryogenes with keratosis of the follicles in general.

DR. PELS: The patient was presented because he had keratosis pilaris on the arms and legs as well as an erythema with nutmeg-grater appearance on the eyebrows and on the cheeks. The question naturally arose whether this was one and the same process, associated as it apparently was with demonstrable endocrinopathy. If this were the case, then it would appear to be an unusual type

of keratosis pilaris. I did not consider ulerythema ophryogenes in the diagnosis, because I had the impression that this disease is usually followed by scarring, and no scarring is present.

FAVUS. Presented by DR. ROBINSON.

A. L., a Jewish school girl, aged 17, presented over the scalp, particularly on the parietal and occipital areas, seven variously sized, well defined patches, varying from 3 mm. to 2.5 cm., partially bald and pinkish and covered over the surface with numerous small crusts, especially around the follicular openings. There was a moderate amount of infiltration and scarring. The condition had been present for about four years. To the patient's recollection several of these lesions started at one time, and had continued with slow growth to the time of presentation. There were no subjective symptoms. She had lately received a few treatments with ultraviolet light. Folliculitis decalvans was at first considered as the diagnosis until the organism of favus was found.

PARAPSORIASIS. Presented by DR. ROBINSON.

H. L., an American, a die maker, aged 38, presented on the inner sides of the thighs and legs and the inner side of the right arm several well defined, roundish, pinkish, slightly scaly patches, varying in size from 1 by 2 to 2 by 3.5 cm.; no infiltration was present. The physical examination made at the Edgewood Arsenal was generally negative. The condition began about eight months before presentation on the right leg. Other lesions had appeared at irregular intervals, and all had persisted to the time of presentation. Subjective symptoms were practically absent. The administration of salicylic acid in alcohol had no effect.

DISCUSSION

DR. TRAUB: This patient said that he had been taking Ex-Lax almost daily for a long period. Certainly, that phase of the situation should be investigated further. In addition, he has a definite tinea on both feet and his right great toenail is similarly infected. What bearing the ingestion of a phenolphthalein derivative may have on the condition or whether the entire eruption is a tinea can be determined only by further study and observation.

DR. LANE: This case calls to mind two patients whom I have seen recently with rather superficial, sharply defined, reddish-brown plaques such as are seen in this case. One case was found to be associated with a clearcut fungus infection of the feet, and in this case antiparasitic treatment cleared the condition up rather quickly, but it had persisted for several months with mild treatment.

Before I saw the other patient, the case had been presented in Chicago and in Boston. The previous diagnosis had been parapsoriasis, but more recently in Chicago the basal metabolic rate was found to be rather low. Coincident with ultraviolet treatment and moderate doses of thyroid the lesions entirely cleared and remained clear for more than six months; the patient is still taking small doses of thyroid. I believe that the cases which are about to be grouped in the parapsoriasis class need a thorough investigation.

DR. SWARTZ: This case seems to coincide with cases reported by Dr. Charles J. White and myself, which we studied and in which we found the cryptococcus; some cases were described simultaneously by Dr. Cleveland J. White.

DR. WEIDMAN: I agree with the diagnosis. I doubt whether this is a yeast infection, because the latter conditions are moist. In cases described abroad, vesicles almost invariably developed, nearly always in connection with a goodly amount of erythema. The lesions in this patient seem entirely too superficial, even granting that the lesions are superficial in the ordinary type of cryptococcus infection.

DR. SWARTZ: In the cases we studied, the lesions were dry. Few moist lesions were noted, and this moisture was due to secondary infection with some bacterial organism.

ERYTHEMA MULTIFORME BULLOSUM OF DERMATITIS HERPETIFORMIS. Presented by DR. KETRON.

Miss M. W. M., an American, a music teacher, aged 61, presented a generalized eruption over the body, extremities and face, which consisted of discrete or confluent erythematous flat or elevated patches, varying in size from that of a pea to that of a quarter, some of which showed central clearing. Clear blisters ranging in size up to that of a pea were present, occurring alone or occasionally in small groups which soon ruptured, resulting in crust formation. None were found which seemed to arise from an entirely noninflamed base. The palms and soles had a diffuse pinkish color. One or two blisters were seen in the mouth, and at times there was some diffuse reddening of the tongue. The general physical examination revealed moderate arteriosclerosis and hypertension. The tonsils were not definitely diseased but were large. The urine showed a trace of albumin. The blood and differential counts were essentially normal. Roentgen examination of the teeth showed five in which the roots were dead, only one of which gave evidence of bone resorption. (Roentgenograms taken two years previously showed these teeth to be in the same condition as at the time of presentation.) A few infected teeth, however, had been removed two weeks before presentation. Cultures from the root gave a pure growth of *Streptococcus viridans*. The patient's skin was tested with a filtrate of a broth culture of this organism with negative results. Pel's and Macht's phytopharmacologic test was negative. Microscopic observation of one of the vesicles showed a blister which had formed between the epidermis and the cutis. The floor was covered with leukocytes and nuclear fragments, some of which had forced their way beyond the limits of the vesicle along the junction of the epidermis and cutis. There were few eosinophils. A moderate perivascular infiltration was present in the cutis.

The disease had begun four months previously with some blisters on the lip, which the patient thought were fever blisters. Within a few days other lesions appeared on the body, and the eruption soon became generalized. Itching and burning had been annoying features. Otherwise, she felt well and had had no fever. She had taken no drugs previous to the development of the disease.

She received a methenamine preparation and calcium lactate therapy intravenously and acidophilus milk internally. One tooth was removed two weeks before presentation. Despite the elapse of three and one-half months, there had been little improvement in the condition. The erythematous features were not so prominent as in the beginning, and the itching and burning were not so annoying. New blisters, however, continued to occur. The case was presented for suggestions as to treatment and also to clear the diagnosis. Should pemphigus be considered? (Five months later the patient had slightly improved.)

DISCUSSION

DR. HIGHMAN: I think the patient has pemphigus, but one cannot be arbitrary.

DR. FOX: I think this case could be regarded properly as one of dermatitis herpetiformis, in spite of the short history of three months' duration. The fact that there had been a few bullous lesions in the mouth would not exclude the diagnosis of Duhring's disease. The fact that the patient had not lost flesh and strength was against the diagnosis of pemphigus, as was also the evidence of severe itching which she presented. This would certainly be foreign to pemphigus and would also not be in accord with the usual picture of a bullous erythema multiforme.

DR. STRAUSS: It may be possible therapeutically to differentiate in this type of case between dermatitis herpetiformis and erythema multiforme. The intravenous use of mercuric cyanide will cause the disappearance of erythema multiforme, even of the bullous type, in from two to four days and will stop itching if present, whereas, while it may have some temporary effect on the itching and eruption of dermatitis herpetiformis, it will not result in a speedy cure.

DR. STOKES: I believe that this patient has dermatitis herpetiformis. She exhibits strikingly the diagnostic point often mentioned by Dr. Ormsby of intense

burning as distinguished from itching until the vesicle is ruptured. I have confirmed Dr. Ormsby's comments on this point over years of observation and believe that it is a helpful distinguishing feature in these cases on the borderline of erythema multiforme.

DR. WEIDMAN: There are certain features here which resemble those of erythema multiforme, and in that connection I recall the discussion at the recent meeting of the Mississippi Valley Conference (ARCH. DERMAT. & SYPH. **18**:445 [Sept.] 1928) in which similar experiences were related. Wende had described features common to both Duhring's disease and erythema multiforme perstans, and Dr. Pusey thought that cases of this type ought to be called Wende's disease. I have studied a similar case as one of persistent erythema multiforme which from time to time showed allergy-like flareups; there was a similar division in the Philadelphia Dermatological Society as to whether it was Duhring's disease or persistent erythema multiforme. I finally found out that Dr. Schamberg had seen the case a number of years before and that at that time it was a classic case of dermatitis herpetiformis (ARCH. DERMAT. & SYPH. **17**:275 [Feb.] 1928). Perhaps these cases throw some light on the pathologic condition of Duhring's disease, indicating that the etiologic agents are akin to those which produce the disease erythema multiforme. There is not as much pigmentation in Dr. Ketron's case as in Wende's disease, but it might be too early. I still think that this diagnosis should be considered.

LUPUS ERYTHEMATOSUS (?) RESISTANT TO THERAPY WITH UNUSUAL PERSISTENT INVOLVEMENT OF THE MUCOCUTANEOUS AND ORAL SURFACES. Presented by DR. PELS.

M. H., aged 48, a Russian Jewish tailor, did not present evidence of pulmonary or other tuberculosis. The tonsils were enlarged but not diseased. The teeth were in a poor condition and showed pyorrhea, and there was an upper plate. A systolic blow was heard at the apex, but was not transmitted. Lesions were seen on the face, ears, nose, left eyebrow, neck, scalp, lips, tongue and buccal mucosae. There were scars on the left forearm. These lesions occurred as fairly well defined, discrete and confluent patches of a deep red color, measuring up to 4 or 5 cm. in diameter. They were maculopapular, having suggestive keratotic plugs, adherent scaling and atrophy. Leukodermic changes were present on both cheeks and on the sides of the neck; white striations appeared on the lips and on the lesions of the mouth, where there were also erosions. There was some roentgen telangiectasia. The Wassermann reaction of the blood was negative. Biopsy of a lesion of the lip was suggestive of lupus erythematosus. Cultures from the removed tonsils were not recorded. There was a sudden onset, twenty years before presentation, first on the lips, later on the lesions appearing on the nose, face and neck. There were no coincidental infectious diseases, except frequent colds. The patient's health was good, and there were no subjective symptoms. Tonsillectomy was performed three years before presentation, without focal reaction and without improvement in the eruption. Carbon dioxide snow, irradiations with the roentgen rays and ultraviolet light and various ointments were employed, with slight improvement of the lesions. Ten injections of mercurochrome-220 soluble were given intravenously with no results. About two years before presentation a gold compound and sodium thiosulphate, intravenously, were used in doses of from 75 to 500 mg. for a total of sixteen injections over a period of three months. There were some reactions, and considerable improvement was noted. Solution of potassium arsenite and tonics were also given. There was an incomplete cure; the dermatosis has been resistant to therapy, and roentgen irradiations were followed by leukodermic changes.

DISCUSSION

DR. SCHAMBERG: I must confess that marked involvement of the mucous membrane of the mouth is extremely rare in lupus erythematosus. A little reservation must be expressed as to whether the lesions of the mouth are really

due to the underlying condition or represent the buccal lesions due to the administration of a gold compound. Such lesions of the mouth after the use of a gold compound are not rare. According to the history, this patient received a number of injections of a gold compound, varying in dosage from 75 to 500 mg. The therapeutic reactions of patients to treatment with a gold compound vary greatly. Some who are treated with injections week after week in the same dosage may have their cells so habituated to the metal that the full therapeutic effect is not obtained. In some cases it is better to increase the dose considerably and increase the interval between injections in order to produce more of a therapeutic shock. In several patients that I have treated in this manner, the result has been most gratifying.

Then, again, in patients who have received a considerable amount of a gold compound without complete disappearance of the eruption, good results may be obtained at times by substituting neoarsphenamine or, better, sodium silver arsphenamine. In other cases the conjoint use of organic iodine by mouth may prove helpful. In the treatment of a considerable number of patients, I have not seen a single complete failure. By the manipulation of dosage, of the interval of treatment and the use of conjoint measures, one can usually bring about a disappearance of the eruption.

A Case for Diagnosis, with the Question of Onychomycosis of the Toes, and Trophic Changes of the Finger-Nails. Presented by Dr. Pels.

A. B., aged 30, a Jewish woman, presented moderate hypertrichosis. The mouth showed fairly well defined patches of erosion on each buccal surface with whitish striations and a shredlike periphery. All of the nails were affected. The fingers revealed a normal nail-bed; the plates were lusterless, had horizontal ridging, depressions and irregular pittings. They were dry and somewhat brittle; the free edges were normal, and there was no inflammatory change. The toes were similar to the fingers except that the nail-beds were thickened and solid. The tests on the urine and blood, the chemical analysis of the blood, the gastric analysis and the Wassermann reaction of the blood were all negative. The basal metabolic rate was plus 2 per cent. Microscopic examination of the first material from the nails revealed no mycelium, but there were bodies (artefacts?) resembling a cryptococcus (?) found in shavings from the toes. Cultures made on Sabouraud's (dextrose) medium gave no growth. The condition had been present for eighteen months. There was a gradual onset, only one nail being affected in the beginning. The toes were affected last. The patient had no symptoms; however, she was a poor sleeper, had an "acid stomach" and gave indications of "personal maladjustment." Calcium salts and solution of arsenous and mercuric iodide were taken internally. The presentation was made for suggestions as to therapy. Attention was directed to the noninvolvement of the nail-beds of the fingers.

DISCUSSION

Dr. Weidman: The latest information I have on ringworm of the nails is that which Dr. Charles M. Williams brought to me. He had been studying what appear to be normal nails and showed me seventeen cultures of *Hyphomycetes*. In six cases, the same species was obtained from nails as occurred on the skin of the foot, and the others were species commonly occurring between the toes; that is, apparently normal nails serve as another reservoir for fungus infection. Like Dr. Williams, I have found yeast organisms present in the nails also, so one is now confronted with the additional problem of how many of the organisms are to be regarded as pathogens and how many as saprophytes. With the condition in the toes so common, it is not at all surprising that there should be this disturbance in the nails, but Dr. Williams has supplied a great deal of information as to the lesions they do not produce.

Dr. Schamberg: If it is definitely established that the condition of the nail is not due to a fungus, then I should like to suggest another possibility. The

patient has a leukoplakial patch in the mouth. Cases of lichen planus limited to the tongue or to the mouth are common. I have seen several cases of lichen planus of the nails with striations. The question of a possible lichen planus of the nails should not be entirely left out of consideration.

DR. FOX: I do not think that any one could consider this an unquestioned fungus infection. The changes were also not due to paronychia nor to any surrounding dermatoses which might affect the cells of the matrix. The symmetry and involvement of all the nails would, in my opinion, favor the diagnosis of atrophy of the nails from some unknown cause.

DR. SWARTZ: The toe-nails show a yellow to orange discoloration with definite thickening and presence of debris. The interdigital spaces on the left foot show maceration and some scaling. This picture is consistent with the clinical diagnosis of epidermomycosis. In some cases giving such a picture one does not find the epidermophyton organism, but there is present a monilia such as is demonstrated in this case. The dystrophy in the finger-nails reminds me of a similar case in a technician at the Massachusetts General Hospital. In addition, she showed a few scattered scaly erythematous patches on the thighs. A monilia was found in the scrapings from both toe-nails and finger-nails, and I offer one diagnosis instead of two as was suggested.

DR. PELS: This patient was seen by other dermatologists and was told nothing in the matter of diagnosis. The laboratory observations are inconclusive. An interesting fact is that the nail-bed of the fingers is not affected, whereas the nail-beds of the toes are so changed (thickened) as to incline one to the clinical diagnosis of onychomycosis of the toes. It is probable that the apparent trophic disturbance of the plates is the same on the fingers and on the toes, and that the disease of the nail-beds of the toes is incidental.

A CASE FOR DIAGNOSIS. Presented by DR. KEMP.

R. E., aged 3, white, an American, presented large, deep-seated nodules on the legs, buttocks and feet accompanied by infiltrated ulcers from 1 to 4 cm. in diameter, the edges of which were ragged and undermined. The bases were covered with dirty granulation tissue. There was pleural effusion of the left lung, extending to the axilla. There was marked enlargement of the liver and spleen accompanied by a general glandular enlargement. The Wassermann reaction of the blood and the tuberculin tests were negative. Skin tests for *Monilia* and *Sporothrix* were also negative. Inoculations into animals (guinea-pigs, mice and chickens) gave negative results. Cultures from the ulcers were also negative. Biopsy revealed nonspecific granulation tissue.

The general health was good until the age of 18 months. At this time nodular lesions which rapidly ulcerated appeared on the right foot. This condition was accompanied by generalized glandular enlargement. At the same time the patient developed a papulovesicular rash, photophobia, conjunctivitis and an enlargement of the liver and spleen. Roentgenograms at that time revealed a tuberculous osteomyelitis of the first right metarsal bone.

The patient had been under constant observation since that time, and the disease had continually progressed. Treatment had consisted of thymol, ultraviolet light, potassium iodide, internally and locally, tuberculin and neoarsphenamine, all of which had failed to produce any result.

TERTIARY SYPHILIS. Presented by DR. ROBINSON.

W. B. K., aged 52, an American, a packer, had two lesions located on the back of the left hand and wrist. The one on the back of the hand consisted of a somewhat punched-out ulcer with a slightly rolled and elevated edge. The edge showed some scaling, and was bluish red. The base of the ulcer was serosanguineous, with the formation of a slightly purulent slough. The lesion on the wrist was slightly smaller and appeared as a thin atrophic, parchment-like scar with a violaceous border and a few crusts at the edge. On the thenar eminence

there were also a few irregular keratotic edges. The patient had gonorrheal infection fifteen years before presentation. There was no history of a primary sore. The Wassermann (Kolmer) reaction of the blood was 4-4 (repeated). The condition had been present for six weeks. The lesion on the back of the hand began as a papule, which the patient picked. The lesion on the wrist appeared one week later. The patient said that the keratotic lesions on the palm had been present for about six months and had remained unchanged. Locally, only bland ointments had been given. No intravenous therapy had as yet been instituted. The ulcerated lesion when first seen about three weeks before presentation suggested a simple infected sore, echthymatous in character. The scarlike lesion on the wrist was considered syphilitic.

DISCUSSION

DR. ROBINSON: Since the patient's first visit, about two weeks ago, boric dressing have been applied, and the lesions have gradually resolved. The ulcer is much shallower than it was at first, and there has been marked reduction in the infiltration of the nodule. We have waited for this meeting before beginning active, antisyphilitic treatment.

DR. GOODMAN: I recall that when I first saw this patient, the active open sore looked like an ordinary echthymatous lesion. The slightly atrophic, parchment-like scar with a sharp irregular edge on the wrist, however, betrayed the true nature of the condition. The echthyma-like lesion developed an elevated, infiltrated, dull reddish edge with superficial punched-out ulceration revealing a serosanguineous base, not unlike that of a primary sclerosis. On the palm there were irregular, dull reddish keratotic patches. The Wassermann (Kolmer) reaction of the blood showed complete fixation. The interesting feature in this case was the peculiar localization of two types of late syphilitic lesions on the right hand and wrist.

PAGET'S DISEASE. Presented by DR. MOORE.

L. S., a white woman, aged 28, an American, had a masculine distribution of hair. There was a slight thyroid struma. There were marked thickening and anterior bowing of the right tibia, with local heat but no redness, and only slight tenderness. The Wassermann reactions on the blood and spinal fluid were negative. Roentgen examination of the right tibia revealed syphilitic osteitis, and subsequent roentgenograms, especially of the skull, Paget's disease.

In January, 1922, there was painful swelling of the right shin. The roentgen diagnosis at this time was syphilitic osteomyelitis. Since then the pain in the swelling in the right tibia had increased. The husband had tabes, and the patient was examined for this reason. There were five living nonsyphilitic children; there had been one premature stillbirth and one miscarriage at three and one-half months. Two courses of arsphenamine and one course of bismuth were given. Seventeen Wassermann reactions of the blood were negative. There was an increase of pain in the leg, the headache and the pain in the left forefinger. In July, 1926, pathologic section from the tibia revealed normal bone.

This patient had early Paget's disease beginning in one tibia, subsequently involving the skull, and confused with syphilitic osteitis.

DISCUSSION

DR. STOKES: This is certainly a beautiful and surprising picture of pseudo-syphilis, a subject which now needs as much exploitation and study in some diagnostic centers as syphilis itself did a decade ago.

SECONDARY INFECTION WITH SYPHILIS OCCURRING FIVE YEARS AFTER A FIRST INFECTION. Presented by DR. CHESNEY.

C. B., a colored laundress, showed several small ulcerated areas on the cervix and vaginal wall. Biopsy of one of these ulcers revealed chronic inflammatory

tissue. No dark field examination was made. The spinal fluid was normal. Blood culture was negative. The Widal reaction was negative. The blood count was normal. The first infection occurred in 1923. At that time the patient was examined in the syphilis clinic and was found to have secondary syphilis with a positive Wassermann reaction. She was treated for a year, during which time she received alternate courses of arsphenamine and mercury by inunction. The Wassermann reaction became negative, and the spinal fluid was normal. She was then put on probation and followed for more than a year, during which time the Wassermann reaction remained negative. In March, 1925, she had a pelvic operation in another hospital. The pelvic organs were removed, and she was told that she would not menstruate again. On Oct. 11, 1928, vaginal bleeding occurred, and for this reason she was admitted to the gynecologic wards. After neoarsphenamine was given, the temperature dropped abruptly to normal. The lesions healed and the symptoms cleared up. This patient was presented as showing an example of reinfection with syphilis.

PARESIS; SYPHILIS OF THE CARDIOVASCULAR SYSTEM. Presented by DR. CHESNEY.

J. E., a negro laborer, aged 43, was seen in the medical clinic in 1908, at the age of 22, and the condition was diagnosed secondary syphilis. He received a small amount of mercury and potassium iodide by mouth and then disappeared from observation. In 1919, he came to the medical clinic on account of cough. He was admitted to the hospital where roentgen examination of the thorax showed a mediastinal tumor which was thought to be an aneurysm of the transverse arch of the aorta. Both the blood and the spinal fluid gave a positive reaction. He was treated in the clinic for approximately a year, receiving arsphenamine intravenously and mercury by inunctions. He then disappeared from observation. Four years later, he was struck on the head and shortly thereafter began to show mental changes. At an examination in 1925, or six years after the aneurysm was revealed, he was seen again in the syphilis clinic and at that time clinical and roentgen examination showed no signs of the mediastinal mass. In 1928, the patient received sixty-two injections of tryparsamide, twenty-five injections of bismuth and seven injections of silver arsphenamine. The spinal fluid still gave a positive reaction, and his mental reaction was that of a quiet paretic.

This case was of particular interest because of the disappearance, under treatment, of the mediastinal tumor which was originally diagnosed as an aneurysm. The patient was also of interest because the clinic possessed records of him over a period of twenty years.

TERTIARY BONE SYPHILIS, INVOLVING THE SKULL, CLAVICLE AND STERNOCLAVICULAR JOINT. Presented by DR. CHESNEY.

B. B., aged 43, a negro housewife, presented a large defect at the vertex of the skull, in the midline, in the inner table, which was tender on palpation. There was a painless swelling involving the bone and joint at the inner end of the right clavicle. The pupils were unequal and reacted sluggishly to light. There was a diastolic murmur over the base of the heart, and the blood pressure was 180 systolic and 100 diastolic. Roentgen examination revealed: syphilitic osteomyelitis of the right clavicle, Paget's disease of the skull and a dilated aorta. The Wassermann reaction was completely positive; the Wassermann reaction of the spinal fluid was negative; the urine contained albumin. In April, 1928, at the right sternoclavicular joint a "knot" appeared which had increased in size. The hearing of the right ear and the vision of the right eye became impaired. The patient suffered with severe occipital headaches, transient numbness and swelling of the left arm. Treatment consisted of neoarsphenamine, mercury rubs and potassium iodide by mouth. The albumin disappeared from the urine, and a marked improvement in the general symptoms occurred.

DISCUSSION

DR. STOKES: This demonstration of reduction in the size of an aneurysm is the choicest that I have seen, provided, as is undoubtedly the case here, the lesion is an aneurysm and not a mediastinal tumor. Dr. Baetjer's experience as a roentgenologist would of course preclude any mistake. There are, however, references in the literature and mention in my text of similar occurrences, but this report, with its beautiful x-ray plates, is unique in quality if not in priority.

DR. WEIDMAN: I recall a gross morbid specimen of aneurysm from the walls of which globules of metallic mercury could be squeezed; the case was presented before the Philadelphia Pathological Society by Dr. John A. Kolmer and examination was subsequently made by him (*Proc. Path. Soc., Phildelphia* **22**:43, 1920). While tenuous, it might be figured out how many grains of mercury had been administered, if this could have influenced the size of the aneurysm and if the subsequent absorption of the mercury could account for the reduction in the size of an aneurysm.

DR. MOORE: This case, I think, points out the fact that the treatment for cardiovascular syphilis is not entirely futile. I might add that we have three other patients with aneurysms who have remained alive and in good health for periods ranging from seven to twelve years.

NEW YORK DERMATOLOGICAL SOCIETY

PAUL E. BECHET, M.D., *Secretary*

Regular Meeting, Dec. 18, 1928

HOWARD FOX, M.D., *President*

GENERALIZED NEURODERMATITIS. Presented by DR. FRASER.

A woman, aged 20, had a generalized eczema since childhood which was resistant to all methods of treatment. She said that while a child the condition usually improved during the summer when bathing in salt water, but as she grew older such improvement ceased, and the condition remained about the same. When presented there was a generalized dry eczema with considerable pruritus and lichenification.

DISCUSSION

DR. ELLER: I think that this type of eruption belongs in the class with the eczematous eruptions due to allergy. This patient gives a history of repeated generalized eruptions apparently due to some protein sensitization. These patients are most difficult to treat successfully. There is no specific treatment, and no one plan helps all of them. Some are helped by the roentgen rays and the antipruritic salves; others get little relief from this therapy. Then there are some patients who seem to obtain improvement from the internal administration of belladonna. Pulley claims that most of his patients respond to belladonna internally, and believes that in this type of case there is a vagotonia and that the belladonna counteracts this. All treatment known thus far is really empirical, and what will help in one case will fail in another.

DR. WISE: My best results have been obtained by insistence on rest in bed with the application of mild ointments or lotions, and the administration of sedatives internally. I have had no good results with the use of bromides given intravenously.

DR. HIGHMAN: I should like to take issue with Dr. Eller on his conception of allergy. Allergy is not a clinically recognizable condition; hence, it has no place as part of a clinical designation such as "allergic eczema." Allergy is a process, an etiologic, not a diagnostic, concept. It is explanatory, not descriptive.

It applies to a pathogenic mechanism. All eczema is allergic, whether metabolic or infectious in origin, and it is due to a specific reaction to a given agent. Thus, when I hear the word used as Dr. Eller uses it, I, for one, protest, so that readers elsewhere may not imagine all American physicians subscribe to an absurdity, indicating a vague and unscholarly grasp of the phenomena of sensitization.

DR. MALONEY: I agree with Dr. Wise about putting the patients to bed. We have had some patients at Bellevue who were put to bed and they improved — very slowly, but they improved. We have tried bromides with some results.

DR. LANE: I agree with what Dr. Wise has said about the uncertainty of all sorts of treatment in these cases, and should have to have a long series of comparative cases presented before I should be willing to accept any statement in regard to the general efficacy of any treatment. I agree with Dr. Highman that invoking allergy as an explanation for such a case is of little use unless the offending agent can be approximately identified.

DR. HOWARD FOX: I do not think it makes much difference whether one calls this condition lichenified eczema or neurodermatitis. Every one is familiar with this type of eruption, which occurs especially in young girls, on the neck and cubital spaces. In my experience, such cases have been extremely refractory to treatment. I have not found any particular form of treatment to be especially effective. As to calcium chloride urea, I have used this drug chiefly in urticaria, with poor results.

DR. ELLER: I would like to differ with Dr. Highman regarding the term allergy. Just because we cannot state the specific protein to which the patient is sensitive is no reason why the eruption could not be due to protein sensitization. As a matter of fact, in most eruptions due to protein sensitization the specific protein cannot be proved by means of our present methods. There are eruptions, however, which can be definitely proved to be in the allergic class. For example, the numerous cases on record of patients who develop a marked attack of hay-fever after sleeping over night on a hair mattress; on the next attack, the same patient does not get hay-fever, but a generalized pruritic eruption instead, or a combination of both. I do not agree with the men who include under allergy every form of dermatitis venenata, even iodine burns.

DR. HIGHMAN: All inflammation is due to allergy. Hence, all inflammatory skin lesions are — the toxic, the infectious, the metabolic, the physical. Only neoplasms and anomalies of the skin are not, so far as we know, allergic. Moreover, allergy applies equally to protein and nonprotein sensitization, according to the current point of view, and equally to chemical and physical agents. Bloch in Europe and I in America have amply brought out the points involved — that allergy in eczema is the generic explanation of the dermatosis, a definite susceptibility of the skin to a poison. This likewise applies in dermatoses due, for example, to the sun. The rays elicit a toxin, or raise the skin's susceptibility to toxins otherwise produced. This is allergic as much as if corrosive mercuric chloride, formaldehyde or a protein were the agents. What is involved is a matter of fact, a clear understanding of fact, and not a matter of Dr. Eller's opinion. Knowing this much is the major part of the problem to be solved. Dr. Eller's conception of allergy reminds me of a woman who consulted me and said, "I wonder if you can treat metabolism."

DR. FRASER: I thank the members for their suggestions as to treatment. I have tried almost everything I have ever heard of without any apparent beneficial results. As usual in cases of the kind no useful information was gained from the various laboratory tests.

CHONDRODERMATITIS NODULARIS CHRONICA HELICUS. Presented by DR. HOWARD FOX.

I. K., an unmarried woman, aged 31, born in the United States, a stenographer, had suffered from painful nodules of the ears for four years. The eruption had originally consisted of bilateral small, painful, tender nodules, the size of a pea,

symmetrically situated on the central and most prominent parts of the anthelix of the ears. The lesion on the right ear had been treated by electrodesiccation two years previously. The pain and tenderness had disappeared as a result, though the scar was somewhat red and not good from a cosmetic standpoint. The left ear had been treated with unfiltered roentgen rays (two and one-half skin units) with no permanent benefit. The patient was a well nourished young woman in apparent perfect health.

DISCUSSION

DR. THRONE: I should suggest surgical excision.

DR. LANE: There is no question that this patient has a chondrodermatitis. For several reasons, however, I do not think that it belongs in the group of cases known under the name of chondrodermatitis nodularis chronica helicis. In the first place, the lesion is located on the anthelix and not on the helix. Foerster noted that a striking feature is the uniformity with which the lesions of chondrodermatitis nodularis chronica helicis are located on the upper border of the ear in the region of the crown angle and on or near the free folds of the helix. In the second place, in the twenty-one cases collected by Foerster the condition has been seen only in adult males. Finally, in this case I think the cause can be positively stated to be pressure. This is not the case in the typical chondrodermatitis nodularis chronica helicis. The patient says that the sores developed while wearing one of the tight helmet hats which press over the ears, and I have no doubt they started as pressure sores. I have not seen this condition reported anywhere, but I have seen several cases in which the cause was, as in this case, definitely shown to be pressure. The first cases that I saw were in nuns in whom the pressure exerted by the stiff starched bands that are worn under the hoods was the cause. I have recently seen a young girl with a lesion on one ear similar to that in the case presented, in whom the pressure was exerted, as in this case, by a tight helmet hat. The location on the most prominent point of the helix is as typical for this condition as the location on the edge of the helix is for the previously described chondrodermatitis nodularis chronica helicis. These lesions are as slow about healing as the chondrodermatitis nodularis chronica helicis, and in order to secure any results with any sort of treatment all the pressure must be kept off the site of the lesions indefinitely.

DR. BECHET: Some consideration ought to be given to Dr. Lane's remarks. I have seen only a few cases presented with this diagnosis, one by Dr. Wise some years ago, and in them the lesions were on the helix. In the case presented tonight, the lesions are exactly symmetrical on the anthelix, exactly where the greatest pressure would be made by a hat.

DR. HOWARD FOX: I have another case under observation in which the condition is precisely similar to the one presented. This would accord with Dr. Lane's suggestion of pressure, the patient ascribing her trouble to wearing tight hats. She obtained relief by wearing larger hats.

The fact that these lesions are not on the exact part of the ear (the helix) as originally described makes no difference to the fact that it should be classed under the foregoing title. It is a painful nodule of the ear whether on the helix or on the anthelix.

A CASE FOR DIAGNOSIS (LYMPHANGIOMA?). Presented by DR. WILLIAMS.

The patient, an infant, aged 7 months, had a lesion that was first noted when the child was only a few days old, which had persisted since that time. Examination showed a small scarlike mass on one wrist on which a hemorrhagic vesicle formed from time to time, then dried. There was no other lesion on the body. This lesion had been observed both when fairly dry and when filled with sanguinolent fluid.

DISCUSSION

DR. TRAUB: The infant has been brought to the clinic three or four times. On the first occasion I thought the condition was a pigmented nevus which had

been treated with carbon dioxide snow and was just healing. The mother, however, said that the infant had had no treatment, but repeated blebs had appeared on the area. After we had kept a sealed dressing over the spot for about ten days, it healed entirely and the patient was discharged.

DR. BECHET: The lesions impressed me also as being neurotic and extraneous.

DR. WISE: I cannot offer any definite diagnosis, but I would discount the idea of an artefact. The mother would not be likely to injure the child. I should offer a tentative diagnosis of lymphangioma circumscriptum, in which the fusion of the lymphatic vessels has caused a large bleb. That is all I can think of in view of the fact that the lesion appeared just after birth.

DR. WILLIAMS: It seems to me to be a nevoid condition, but I have been trying to think of one that would give both serum and blood.

DR. TRAUB: I saw the child on one occasion, at which time the skin was apparently normal, and twenty-four hours later there was a diffuse bleb covering the area in question. It seems to me that this is some type of artificially produced eruption.

DR. WISE: The fact that infants' skin is tender as compared with the skin of an adult with lymphangioma circumscriptum would possibly account for the fusing of the small vessels and the formation of a bleb.

SCLERODERMA (SCLERODACTYLIA TYPE). Presented by DR. HOWARD FOX.

G. B., a married woman, aged 49, born in the United States, first noted the eruption eleven months prior to presentation. It began as "sores" on the knuckles, followed by slight stiffness of the finger joints, and later some difficulty in raising the arms. She had lost 20 pounds (9 Kg.) within the past year. Examination showed a marked tightness of the skin of the fingers and hand, extending in a less degree up the forearm. There was marked contracture of the fingers at the second and third phalanges forming almost a right angle with the first phalanx. The tips of the fingers were pointed. There was no evidence of Raynaud's phenomena. She showed a moderate amount of hidebound skin of the forehead and cheeks, the face being rather expressionless. There was considerable hypertrichosis of the face and a mottled appearance of the upper part of the chest and anterolateral aspect of the trunk, due to pigmentation without any apparent change in the texture of the skin, which was normally of a dark shade. The patient was short and poorly nourished, and was in poor general health. The basal metabolic rate was + 28. The urine showed nothing abnormal. She had been given thyroid medication by another physician for three months without any effect.

DISCUSSION

DR. WISE: The physicians at the Mayo Clinic at Rochester are said to have obtained improvement in these cases following the operation of spinal gangliectomy.

EXTENSIVE RADIODERMATITIS FOLLOWING TREATMENT FOR HYPERTRICHOSIS. Presented by DR. HOWARD FOX.

A. E., a man, aged 31, said that he consulted Dr. A. S. Geyser in the spring of 1923 for treatment for an extensive hypertrichosis of the trunk. He said that roentgen treatment was given to the back two or three times a month for six months. One year later he returned for further treatment, at which time he said the roentgen rays were again used on the back and also on the chest. During the course of treatment, the patient alleged that an acute inflammation with open sores occurred in the regions treated, some of which had not completely healed when presented. Telangiectases first appeared between from twelve to eighteen months after the last treatment had been given. He presented an extensive and diffuse telangiectasia involving the entire chest (with the exception of scarred areas) and large areas of the back. In the latter region, there were considerable pigmentation, whitish atrophic spots and a few small crusted lesions which had

never healed completely. On the chest there was scarring resulting from treatment by another physician with carbon dioxide snow, and some depigmented round areas due to the use of the Kromayer lamp. The patient was in good general health.

DISCUSSION

DR. HOWARD FOX: I wrote to Dr. Cramp of the American Medical Association, and he said he would include this case when writing up the question of roentgen treatment for hypertrichosis by advertising physicians. He said that this case, although the patient was treated by Dr. Geyser before he started the Tricho Institute, should be included in the record of patients treated by him. It is one of the worst of the kind I have seen.

DR. THRONE: It seems that the Department of Health has a certain supervision over these so-called "X-ray Laboratories." Would it not be possible by some means to have the matter taken up by them?

DR. HOWARD FOX: I attended the meeting of the Department of Health when this subject was discussed, and was informed that nothing could be done with these men, in view of the fact that they were licensed physicians.

A CASE FOR DIAGNOSIS. PRURIGO NODULARIS OR HYPERTROPHIC LICHEN PLANUS. Presented by DR. TRAUB.

W. C. H., a married man, aged 53, born in the United States, presented an eruption which had been present from two to three years, but in an aggravated form only for one year. He had nodules on the lower parts of both legs, with a few isolated ones on both wrists. The nodules were warty and discrete and were covered by some scaling, but crusts formed only when the lesions were severely scratched. The results of urinalysis were negative. No biopsy examination was made.

DISCUSSION

DR. WISE: I do not agree with the diagnosis of prurigo nodularis. I think the probable diagnosis is lichen planus hypertrophicus. In prurigo nodularis the lesions are farther apart, usually larger, more nodular, more elevated and there is more crusting. The reasons for believing it lichen planus are the distribution of the lesions, the presence of individual small red papules and the fact that the lesions on the outer side of the leg show well defined superficial inflammatory reactions, which do not usually appear in prurigo nodularis.

DR. MALONEY: Dr. Wise might have brought out another point, that most of these cases are in women; this case is in a man. The nodules, too, seemed to be smaller than one would expect to find in prurigo nodularis. I do not exactly disagree with the diagnosis, but certain points do not fit in with it.

DR. WILLIAMS: I agree with the diagnosis. It is true that the lesions are on the whole smaller than those usually seen. On the other hand, I had a patient with smaller lesions. A difference usually must be made between prurigo nodularis and small lichenified tumors which are the result of scratching. The individual lesions arise from a normal skin; the crusting is not present in prurigo nodularis excepting as the result of scratching; the nodules are covered with a rather tough epidermis; the distribution is right for prurigo. The face, arms and legs are the areas on which it usually occurs. Another reason is that the tumors once established never disappear with age, which is the case here. Only a few cases have been reported in men. I should say that this is a case of prurigo nodularis, of only one year's duration, in which the tumors have not yet acquired any size. I think that if the case is followed up, one will find that the tumors become larger.

DR. FRASER: I have had little experience with prurigo nodularis, but I believe that Dr. Wise's conception is correct. It seems to me that some of the papules are characteristic of lichen planus. On the other hand, Dr. Williams has offered serious objections to that diagnosis, viz., the duration of the lesions and the fact that they have never undergone resolution. A biopsy should be performed, and

a slide presented at the next meeting. It is too important a case to be dropped without establishing a diagnosis.

Dr. Howard Fox: This condition, I think, should be classed as a prurigo-like eruption of the type which is seen at times in leukemia or Hodgkin's disease, though in this case both of these diseases are apparently ruled out. It seems to me that if this were lichen planus hypertrophicus, in the three years in which it has existed there would be some tendency at least for the lesions to become confluent and to form patches, especially on the shins. There are few cases of prurigo-nodularis on record, and I think it would be reasonable to class this case as one of that disease. I must say, however, that it is by no means as typical as the one we saw recently at the Baltimore meeting.

Dr. Traub: When I first saw the patient I made a diagnosis of hypertrophic lichen planus and so treated him, but there was no change in the condition. In fact I think the lesions have become larger and more elevated. At no time did I find any lesion that might be called a typical lichen papule. The features which Dr. Williams brought out are all present. The lesions are intensely itchy, discrete, slightly verrucous, not necessarily covered with crusts and are developing in a manner more or less typical of prurigo nodularis. There are a few cases which have been reported in men. I shall take a biopsy and report on the case at the next meeting.

Dermatitis Exfoliativa. Presented by Dr. Wise.

M. S., a man, aged 47, was previously presented before this society on Oct. 23, 1928. The infiltration of the skin on the body had subsided under treatment with ultraviolet rays, but the palmar and plantar keratosis had become progressively worse. The skin of the palms and soles presented an unusual degree of thickening and stiffness. This condition did not respond to any form of treatment known to the presenter. The patient was again brought before the society to obtain suggestions as to the treatment of the palms and soles.

DISCUSSION

Dr. Highman: I saw the condition in one case of this sort disappear spontaneously after the patient, an elderly gentleman, insisted on having his teeth extracted. In all other patients so treated there was no success. I have seen one or two patients recover spontaneously.

Dr. Kingsbury: I suggest the constant application of hydrous wool fat.

Dr. Throne: I have seen a few of these patients recover following treatment with parathyroid; how it acts, I have not the least idea. It was given for some time and gave fairly good results.

Dr. Howard Fox: Although Dr. Wise appears to have tried nearly every likely remedy, I should suggest a modified Dreuw's ointment, which I have used with success of late in thickened keratotic and other lesions. The remedy consists of salicylic acid, 10 per cent, and chrysarobin and rectified oil of birch tar, each 20 per cent, in petrolatum. I have omitted the soap in Dreuw's ointment owing to difficulty in making a sufficiently firm ointment. To get the best action this salve should be covered by rubber gloves.

Dr. Wise: I will try the parathyroid medication suggested by Dr. Throne.

Tinea Barbae Involving the Upper Lip. Presented by Dr. Williams.

Mr. K., aged 44, said that the condition began five weeks previously. He presented a severe suppurating tinea barbae, involving the upper lip, cheeks and chin. Mycelia were demonstrated from both the upper lip and the left jaw. The temperature on admission was 101 F. The left submaxillary nodes were slightly enlarged and tender. There was no dermatophytide.

The treatment consisted in wet dressings of boric acid; two half unit doses of the roentgen rays, one week apart, and three injections of sodium thiosulphate — resulting in considerable improvement.

DISCUSSION

DR. TRAUB: I treated the patient with the roentgen rays. In the ordinary sycosis vulgaris, particularly when considerable pus is present, one usually gets a tremendous flare up. This man had two half unit doses four days apart, and improved materially, with no reaction.

DR. HIGHMAN: One of the interesting features is the fever of the patient. It is unusual, so far as I know, in such cases. I do not doubt it can be explained by further observation. Dr. Williams may remember a case of favus reported by Lang, of Vienna, in which even the liver was involved. We have to assume that the report of this case was correct, even in spite of the crude methods of verifying that sort of thing in those days; however, it would be interesting to see if this patient has the same fungus in the feces as in the skin. It would also be interesting to give him manganese butyrate. It might be well worth trying.

DR. MALONEY: I should like to ask Dr. Williams why he gave this patient sodium thiosulphate?

DR. HOWARD FOX: One good reason for showing this case is the rarity of such lesions on the upper lip. I cannot recall having seen a similar one. I have been looking for cases of this type of ringworm of the beard for cultural purposes and agree that they are rare in New York. I should like to ask Dr. Williams if he planted hairs, scales or pus in making his cultures. Sabouraud stated that cultures from hairs are less apt to be positive than those obtained from scales or pus.

DR. WILLIAMS: Several points interested me very much. As Dr. Fox says, the case was shown principally on account of the involvement of the upper lip. We found mycelia in a crust from the upper lip, and in a hair from under the chin. We planted hair, pus and crusts — everything. We also plated blood, and made half a dozen plates, but obtained no growths.

The second feature was the fever. I was glad to hear that mentioned in the discussion. A year ago I looked up what had been written on kerion and fever, and fever is mentioned only in two American textbooks, Pusey and Sutton. I think that is an oversight. I believe that in every case of severe tinea or kerion one will find fever. Fever and constitutional symptoms are fairly common. Dr. Highman spoke of generalized favus involving the liver. I have not heard of it, but it is likely, for various tricophytons and achorions have all been recovered from the blood. Within a year, White has demonstrated trichophyton interdigitale from the inguinal node of a patient with tinea pedis; so it is possible for a man to have a generalized infection with any type of ringworm. I considered a biopsy or cutting out a lymph node, but I do not like to do it. At present he is improving.

Dr. Maloney asked why I used sodium thiosulphate. I wanted to do something, and a sulphur compound might make the skin unfavorable for the growth of a fungus. The next remedy I intend to try is a compound solution of iodine, for Ravaut has reported good results from that.

Some one asked if the progress of the condition in these cases is not fairly rapid; I do not think so in cases of ringworm of the beard. Why it should be I do not know. Kerion of the scalp clears up in a few weeks, with wet dressing. All patients get well; apparently, they develop enough antitoxin to cure them. Kerion of the beard, although it may produce fever as in this case, does not clear up quickly; it is sometimes very resistant. It is a clinical fact that I do not understand. I do not understand why it is so hard to cure a child of ringworm, while cattle, horses and dogs get well following treatment with inunction of iodine.

DR. HOWARD FOX: Has Dr. Williams any explanation as to why this disease is so rare on the upper lip?

DR. WILLIAMS: I have none.

DR. THRONE: Dr. Feit claims that he has seen few cases of ringworm of the beard in this country, while in Germany it is common. Is there any explanation for that? Is there a species of ringworm there which we do not see in this country?

A Case for Diagnosis. Pityriasis Rubra Pilaris. Presented by Dr. Traub.

Mrs. M. T., aged 59, born in the United States, presented an eruption which began about June, 1928, first appearing on the forehead. The eyelids next became red and swollen, and the eruption then spread down on the neck, breasts and trunk. The condition on the upper portion of the body apparently cleared up slightly as the legs, arms, feet and hands became involved. There was a moderate amount of scaling in the scalp. There was a general follicular involvement with thick infiltrated red plaques, the irregular outline and fine scaling being most prominent on the knees and elbows.

DISCUSSION

Dr. Wise: I agree with the diagnosis.

Dr. Fraser: I believe that the diagnosis of pityriasis rubra pilaris should not be accepted without question. In the first place, the characteristic discrete hyperkeratotic papules with central horny puncta that we usually see on the dorsa of the hands are entirely lacking; the second point is that there are no lesions on the scalp.

Dr. Bechet: I agree with the diagnosis as presented, but the patches on the back of the hands do suggest psoriasis — they are serpiginous, and are made up of isolated scaly patches. The diagnosis of pityriasis rubra pilaris, however, is the most plausible.

Dr. Howard Fox: I agree with Dr. Wise and consider this an undoubted case of pityriasis rubra pilaris. The remark of Dr. Bechet that it suggests psoriasis does not lessen the probability of its being pityriasis rubra pilaris, as some patients with this disease present scaly patches on the elbows and knees and elsewhere which closely simulate psoriasis. The punctate papules on the border of the scaly patches and the thickening of the palms are characteristic. The absence of keratotic plugs on the backs of the fingers and the pityriasis of the scalp do not change my opinion of this case.

Dr. Traub: When these patients come in early, the diagnosis is not so easy; however, the hands are usually typical in this disease. The follicular plugs generally found on the backs of the fingers are lacking so far in this case. The lesions on the body and the general picture otherwise seem characteristic.

Granuloma Annulare. Presented by Dr. Traub.

Mrs. I. K., a woman, aged 60, born in Russia, presented an eruption of somewhat more than a year's duration, which was limited to the hands and forearms. She had several typical patches near the base of the second and third fingers, representing segments of an incomplete circle. The borders were distinctly raised, and in some places could be seen to be made up of individual papules. There was little transparency or ivory sheen to be noted in these lesions, the color being from brownish to a dull red. The patient received four filtered roentgen treatments, practically all of the lesions disappearing at the same time. They returned, however, and had failed to respond to one unfiltered and three more filtered treatments.

Granuloma Annulare. Presented by Dr. Traub.

W. M., a boy, aged 19, born in the United States, showed a condition which began six months previously. He presented an infiltrated, annular, raised plaque on the dorsum of the left hand near the metacarpophalangeal articulation, 2.5 cm. in diameter. The lesion was slightly deeper in color than the normal skin. The histology suggested leukemia.

DISCUSSION

Dr. Wise: I think the lesion resembles erythema elevatum diutinum. I recall a similar eruption described by the late Dr. Trimble in the Archives of

DERMATOLOGY AND SYPHILOLOGY.

DR. HIGHMAN: The slide presented a true intralymphatic and perilymphatic infiltration, such as one sees in leukemia, and I think this disklike single lesion is the precursor of other lesions that will develop into one of the lymphatic cutaneous syndromes. Whether it will prove to be real leukemia cutis, whether it is a case of mycosis fruste described by Brocq or whether it is a sarcoid of the Spiegler Fendt type, I do not know; however, I do not think it is granuloma annulare or erythema elevatum diutinum.

DR. MALONEY: My impression was like that of Dr. Wise, that it does not seem to be a typical granuloma annulare. We have an elevated disk, which would fit in with erythema elevatum diutinum, which is really a type of granuloma annulare.

DR. WILLIAMS: When I first saw the case I was not in favor of the diagnosis of granuloma annulare, but a closer inspection made me incline to that diagnosis. If one examines carefully with the finger, one comes to a distinct wall of infiltration which is thicker at the periphery than at the center, and it has an irregular circumference.

DR. LANE: I should not be willing to make a clinical diagnosis. I think it must be made by histologic examination. It seems to resemble a sarcoid.

DR. MILES (by invitation): Has the patient an abnormal blood count?

DR. FRAZER: I saw the slide and think that the suggestion of Dr. Highman should be seriously considered. What we have is foci of lymphocytes in lymph vessels, which suggests the histologic picture of leukemia. As to sarcoid, clinically, I agree that there is some resemblance to that condition, but I should be inclined to rule out sarcoid on histologic grounds.

DR. HOWARD FOX: It seems to me that the distinction between granuloma annulare and the disease described by Crocker and Williams as erythema elevatum diutinum is an academic one. There is no important difference between them. The differentiation of granuloma annulare and leukemia is a different matter, and we should all like to hear a report of further study of this case.

DR. TRAUB: The term erythema elevatum diutinum is merely a subheading or rare variety of granuloma annulare. This lesion is made up of distinct papules, and the border is elevated above the center of the lesion. The patient has been seen only once, and I did not go into the question of the blood picture, but will be glad to do so and report at the next meeting.

LICHEN PLANUS HYPERTROPHICUS. Presented by DR. BECHET.

A. F., a man, aged 57, had lesions on the lower part of the legs for twelve years. They first appeared on the ankles, and in four or five years involved most of the legs. These lesions were nodular and so closely aggregated as to form sheets of eruption covering most of the legs. There were no scratch marks, and the coloring was somewhat violaceous. The lesions did not itch.

DISCUSSION

DR. BECHET: The lesions are nodular and so numerous that they are bunched together like grapes, giving a corrugated appearance to the involved patches, which cover most of the lower half of both legs. This symptomatology might fit either neurodermatitis circumscripta (lichenification) or lichen planus hypertrophicus. A biopsy would probably give us the correct diagnosis, and this will be done immediately.

NOTE: The microscopic report was hypertrophic lichen planus.

DR. FRASER: I think that the condition is lichen planus verrucosa.

DR. WISE: I think that the lesion is hypertrophic lichen planus. The appearance is similar to the eruption described by Lieberthal of Chicago in the *Journal of Cutaneous Diseases.*

DR. HIGHMAN: I agree with Dr. Wise that it is in the lichen family. I believe it is typical lichen planus, and I think that if examination is made of one of the small lesions near the knee, it will be found histologically to be lichen planus.

DR. LANE: I agree with Dr. Highman and Dr. Wise that this is not a neurodermatitis, or better, the chronic circumscribed nodular lichenification of Brocq-Pautrier or hypertrophic lichenification. While this condition occasionally replaces the ordinary neurodermatitis, it rarely does so. In this case there are no signs of the lesion having developed on a preceding ordinary neurodermatitis.

DR. HOWARD FOX: The case mentioned by Dr. Wise was described by Lieberthal as lichen ocreaformis or shin guard lichen. It suggests the picture of his case and also cases described as lichen obtusus. I think there is considerable doubt as to how these cases should be classified.

CLEVELAND DERMATOLOGICAL SOCIETY

H. J. PARKHURST, M.D., *Reporter*

Regular Meeting, Dec. 27, 1928

C. G. LAROCCO, M.D., *Presiding*

A CASE FOR DIAGNOSIS. Presented by DR. COLE and DR. DRIVER.

R. S., a negro, aged 22, had two small penile lesions about five weeks before presentation, which had healed spontaneously in about two weeks. Soon after the onset, the inguinal lymph nodes had begun to enlarge, and this enlargement had steadily increased up to the time of presentation. The patient had several attacks of gonorrhea, and a penile lesion in 1926. The Wassermann reaction was strongly positive. The formol-gel test was strongly positive. A biopsy specimen had been taken from the right groin. Smears from the inguinal tumors showed a few organisms suggestive of Donovan bodies.

DISCUSSION

DR. MISKJIAN: I believe that this is a case of lymphogranulomatosis inguinale.

DR. COLE: I agree with the diagnosis. If this condition is lymphogranulomatosis inguinale, it is the earliest case I have ever seen.

DR. RAUSCHKOLB: It may be possible that the lymphogranulomatosis inguinale is engrafted on granuloma inguinale.

LUPUS VULGARIS; TUBERCULOSIS OF SOFT PALATE. Presented by DR. COLE and DR. DRIVER.

G. C., a girl, aged 7, presented an irregular scaling patch on the left cheek, of four months' duration; radium had been applied. The area was slightly thickened. The mucous surface of the left nostril was studded with small reddish-white nodules, and there was a slight mucinous discharge. The right nostril was apparently normal. The mucosa of the hard and soft palates was covered with a similar eruption. The affected areas were not painful or tender. Roentgenologic studies revealed no sign of pulmonary tuberculosis. The tuberculin test (1:10,000) was slightly positive. A younger sister had died of pulmonary tuberculosis. Applications of radium were being used, and injections of gold sodium thiosulphate, together with a high caloric diet, cod liver oil and ultraviolet light. There had been a slight improvement.

A CASE FOR DIAGNOSIS. Presented by DR. COLE and DR. DRIVER.

Mrs. E. S., aged 60, presented a symmetrical, pruritic eruption on the arms, legs and flanks, composed of follicular keratoses. Several giant cells had been found in sections.

DISCUSSION

DR. FISHER: Although there is no involvement of the scalp and hands, the follicular papules over the body suggest pityriasis rubra pilaris.

DR. RAUSCHKOLB: The microscopic picture suggests tuberculosis.

DR. COLE: The giant cells in the section are of the foreign body type and need not point definitely to tuberculosis. The hyperkeratosis and perifollicular lymphocytic infiltration is suggestive of pityriasis rubra pilaris.

HYDRADENITIS SUPPURATIVA. Presented by DR. COLE and DR. DRIVER.

L. J., a negro boy, aged 3 years, since shortly after birth had had an infection of the axillae, with occasional slight exacerbations. The axillary skin was thickened and lay in folds. There were small purulent foci and a mucinopurulent discharge moistened the surface. There was considerable subcutaneous edema. A biopsy examination showed an inflammation of the sweat glands.

A CASE FOR DIAGNOSIS. Presented by DR. COLE and DR. DRIVER.

M. M., a girl, aged 6 years, presented a vesicular and crusted eruption, intensely pruritic, on the arms and legs, of two years' duration, which had resisted treatment with local applications. The observations on the urine and blood picture were normal.

DISCUSSION

DR. NETHERTON: Did the eruption have any relation to vaccination? The clinical appearance of the eruption suggests dermatitis herpetiformis or pemphigus, possibly following vaccination.

DR. COLE: There has been some improvement at times. I thought the eruption was an infectious eczematoid dermatitis.

DR. RAUSCHKOLB: No vegetable parasite was found in the lesions. Chemical investigations of the blood showed no abnormality.

DR. FISHER: I suggest that protein sensitization tests be used.

DR. DRIVER: The clinical appearance of this eruption suggests a circumscribed type of seborrheic dermatitis. It may become a psoriasiform type of seborrheic dermatitis.

DR. NETHERTON: Did the patient ever have crops of bullae on an inflammatory base?

DR. RAUSCHKOLB: No.

KERATODERMA BLENORRHAGICA. Presented by DR. COLE and DR. DRIVER.

L. C., a laborer, aged 28, had been shown at the meeting of Nov. 22, 1928, which was reported in an earlier issue of this journal. Since that time gram-negative intracellular diplococci had been found in a smear taken from the base of one of the crusted lesions on the leg. Similar organisms were found in pus from a small abscess on the forehead.

DISCUSSION

DR. RAUSCHKOLB: The organism was found in the serum after the keratotic crusts were removed. Blood cultures were negative.

GUMMA OF THE LIP. Presented by DR. CARSON.

A widow, aged 66, presented a round patch, of six weeks' duration, on the right side of the upper lip, on the vermilion border. The patch was about 2 cm. in diameter and sharply outlined, with an infiltrated nodular border and an atrophic, scaling center. The dark-field examination had been negative, and the Wassermann reaction had been found negative once, and strongly positive once.

DISCUSSION

DR. RAUSCHKOLB: I consider the condition gumma.

DR. BARNEY: There are nodules, the size of a glass pinhead, grouped in annular configuration. I believe that the condition is a nonulcerative type of gumma.

TUBERCULOSIS OF THE SOFT PALATE, FAUCES AND NASOPHARYNX. Presented by DR. COLE and DR. DRIVER.

J. P., a laborer, aged 47, had complained of sore throat and difficulty in swallowing for three months; he had been losing weight for about five months, and roentgenologic studies had shown advanced bilateral pulmonary tuberculosis. The organisms had not been found in the sputum. There was extensive ulceration of the soft palate, fauces and nasopharynx.

A CASE FOR DIAGNOSIS. Presented by DR. BASKIN.

A girl, aged 18, employed in a rubber tire factory, had had about twelve extensive outbreaks of petechial hemorrhages since July, 1928. Although apparently in excellent general health, she had had some "joint pains." The tonsils were infected.

DISCUSSION

DR. CUMMER: Has this patient any cardiac lesion?

DR. BASKIN: There is no clinical evidence of involvement of the heart.

DR. COLE: I believe that this is a case of purpura, which should be studied thoroughly by an internist.

DR. NETHERTON: The tonsils are rather large. I suggest that they be investigated as a possible focus of infection.

DR. LAROCCO: In the more severe forms of purpura, blood transfusions are of distinct benefit.

A CASE FOR DIAGNOSIS. Presented by DR. LEVINE.

A girl, aged 16, presented a dusky red, infiltrated, scaling eruption, with considerable atrophy on the hands, and especially on the palms, between the toes, around the vulva and under the arms. The condition had begun in November, 1926, on the left hand.

DISCUSSION

DR. FISHER: I consider the condition a case of psoriasis.

DR. COLE: The chronicity of the process, its failure to respond to treatment and, in addition, the small pustules in the border suggest a diagnosis of dermatitis repens.

DR. MISKJIAN: I believe that the condition is psoriasis.

DR. GILLESPIE: I consider the condition dermatophytosis, as suggested by the miliary vesicles in the border of the lesions.

TUBERCULOSIS ORIFICIALIS. Presented by DR. COLE and DR. DRIVER.

R. F., a laborer, aged 35, had pulmonary tuberculosis for at least four years. For two years there had been an indolent, undermined ulcer near the left oral commissure.

CHANCROIDS BENEFITED AFTER AUTO-INOCULATION. Presented by DR. COLE and DR. DRIVER.

J. P., aged 37, had a penile sore and a right inguinal bubo, in which Ducrey bacilli were found. On Dec. 11, 1928, the left thigh was inoculated with pus, and after six days Ducrey bacilli were found in the new lesion. There was considerable improvement in the original lesions.

C. B., a negro, with penile and inguinal ulcerations and a suspected ulcer on the right thumb, had submitted to auto-inoculation with benefit. Ducrey bacilli had been found.

RADIODERMATITIS. Presented by DR. LITTMAN.

E. R., a man, aged 43, had received roentgen treatment for an infection on the back of the neck, eleven years before presentation. He complained of redness in the affected area. There was a typical postroentgen atrophy.

PERIFOLLICULITIS CAPITIS ABSCEDENS ET SUFFODIENS. Presented by DR. BARNEY.

J. S., a negro, aged 20, complained of lumps in the scalp, and said that the process had begun six months before presentation as "little pimples," gradually spreading. Involving the scalp, especially the crown, were numerous globular swellings, varying in size from that of a split pea to that of an olive, joined by sausage-shaped tumescences. There was a partial alopecia over the swellings. On palpation most of these tumors fluctuated, but a few were hard and gave the impression of keloids. Pressure on the fluctuating tumors caused pus to be expressed usually from an opening at a slight distance from the point of pressure. The openings could be probed to varying distances, revealing the fact that the nodules were communicating. There was no marked inflammatory reaction. The cervical lymph nodes were palpable, varying in size from that of a small pea to that of a cherry.

DISCUSSION

DR. BARNEY: If possible, a thorough study of the condition will be made. I believe that in its clinical appearance this case parallels the one reported by Wise and Parkhurst in the ARCHIVES (**4**:751 [Dec.] 1921), under the title of "A Rare Form of Suppurating and Cicatrizing Disease of the Scalp."

DR. RAUSCHKOLB: I should like to see the effect of foreign protein therapy on this condition.

ACUTE GENERALIZED LICHEN PLANUS. Presented by DR. COLE and DR. DRIVER.

H. H. presented a generalized eruption of violaceous angular papules, many of which were shiny, with depressed centers. There were also punctate whitish lesions of the buccal mucosa. The eruption had appeared suddenly, and was of two months' duration. Roentgen therapy had just been used in the dorsolumbar region, following the technic of Gouin.

TULAREMIA. Presented by DR. COLE and DR. DRIVER.

A. F., a negro, aged 32, had cut his left index finger with a rabbit bone four weeks before presentation, while cleaning rabbits. Two days later he had gone to bed with "influenza." Soon the wound in the finger had become purulent, a punched-out ulcer appeared, and at the same time a chain of tender nodules had appeared along the arm, extending to the axilla. On the dorsum of the middle phalanx of the left index finger was a small punched-out ulcer. Extending up the dorsum of the forearm and arm was a chain of nodules, the size of a split pea. There was a nodule the size of a walnut at the insertion of the deltoid muscle, and another in the axilla. Until December 18, there had been an irregular elevation of the temperature, up to 39 C. (102.2 F.); since then it had been normal. The ulcer was healing; the nodes had not ulcerated and were decreasing in size. The patient's serum agglutinated *B. tularense* in a dilution of 1:40. The Wassermann reaction was strongly positive. The leukocyte count was 12,500.

Directory of Dermatologic Societies *

NATIONAL DERMATOLOGIC SOCIETIES

AMERICAN DERMATOLOGICAL ASSOCIATION

Joseph Grindon, President, 4500 Olive St., St. Louis.
C. Guy Lane, Secretary, 416 Marlborough St., Boston.
Place: San Francisco. Time: July 1-3, 1929.

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON DERMATOLOGY AND SYPHILOLOGY

Jay Frank Schamburg, Chairman, 1402 Spruce St., Philadelphia.
William H. Guy, Secretary, Jenkins Arcade, Pittsburgh.
Place: Portland, Ore. Time: July 8-12, 1929.

BRITISH ASSOCIATION OF DERMATOLOGY AND SYPHILOLOGY (CANADIAN BRANCH)

D. King Smith, President, 122 Bloor St. West, Toronto.
E. J. Trow, Secretary, 122 Bloor St. West, Toronto.

LOCAL DERMATOLOGIC SOCIETIES

LOS ANGELES COUNTY MEDICAL ASSOCIATION, DERMATOLOGIC SECTION

George F. Koetter, Chairman, 1136 W. 6th St., Los Angeles.
H. Sutherland-Campbell, Secretary, 1936 Wilshire Blvd., Los Angeles.

SAN FRANCISCO DERMATOLOGICAL SOCIETY

Ernest Chipman, President, 350 Post St., San Francisco.
H. J. Templeton, Secretary, 3115 Webster St., Oakland.

ATLANTA DERMATOLOGICAL SOCIETY

Jack W. Jones, President, Medical Arts Bldg., Atlanta, Ga.
Francis Jones, Secretary, Medical Arts Bldg., Atlanta, Ga.

CHICAGO DERMATOLOGICAL SOCIETY

Harry R. Foster, President, Colby-Abbott Bldg., Milwaukee.
E. A. Oliver, Secretary, 55 E. Washington St., Chicago.

IOWA AND WESTERN ILLINOIS DERMATOLOGICAL ASSOCIATION

Robert E. Jameson, President, 1015 First National Bank Bldg., Davenport, Iowa.
A. T. Leipold, Secretary, 1419½ 5th Ave., Moline, Ill.

LOUISIANA DERMATOLOGICAL SOCIETY

Ralph Hopkins, President, 124 Barome St., New Orleans.
Thomas A. Maxwell, Secretary-Treasurer, 1119 Union Indemnity Bldg., New Orleans.

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* Secretaries of dermatologic societies are requested to furnish the information necessary for the editor to make this list complete and to keep it up to date.

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